U.S. FOOD AND DRUG ADMINISTRATION

MEDICAL DEVICES ADVISORY COMMITTEE

ORTHOPEDIC AND REHABILITATION DEVICES PANEL

Friday, June 2, 2006

ATTENDEES

JOHN S. KIRKPATRICK, M.D.	CHAIR
STUART B. GOODMAN, M.D., Ph.D.	VOTING MEMBER
CHOLL W. KIM, M.D., Ph.D.	VOTING MEMBER
JAY D. MABREY, M.D.	VOTING MEMBER
SANJIV H. NAIDU, M.D., Ph.D.	VOTING MEMBER
PAMELA W. ADAMS, MS, RAF, CQM	INDUSTRY REPRESENTATIVE
CONNIE WHITTINGTON, MSN, RN, ONC	CONSUMER REPRESENTATIVE
LEON LENCHIK, M.D.	DEPUTIZED VOTING MEMBER
ROGER M. NELSON, Ph.D.	DEPUTIZED VOTING MEMBER
KATHLEEN J. PROPERT, Ph.D.	DEPUTIZED VOTING MEMBER
CEDRIC WALKER, Ph.D., PE	DEPUTIZED VOTING MEMBER
JANET L. SCUDIERO, M.S.	EXECUTIVE SECRETARY
MARK N. MELKERSON, M.S.	DIRECTOR, DGRND

CALL TO ORDER

Dr. John Kirkpatrick called the meeting to order at 8:29 a.m. He recognized the Division's 30th anniversary and the Food and Drug Administration's (FDA's) 100th anniversary and announced tentative Panel meetings on October 12-13 and December 11-12.

He stated that at this meeting the Panel will make a recommendation to the FDA on the reclassification of the non-invasive bone growth stimulator (BGS) indicated for the treatment of established non-union fractures acquired secondary to trauma and for use as an adjunct to the treatment of lumbar spine fusion surgery at one or two levels. The Chairman noted the presence of a quorum and asked the Panel members to introduce themselves.

Ms. Janet Scudiero read the statements for the appointment of temporary voting members and conflict of interest Drs. Lenchik, Nelson, Propert, and Walker were appointed as temporary voting members. All members of the Panel were in compliance with the federal ethics and conflict of interest laws.

DIVISION UPDATE

Mr. Neil Ogden, Chief, General Surgery Devices Branch (GSDB) briefed the Panel on significant events since the September 2005 meeting. Three premarket approval applications (PMAs) were approved: St. Francis Medical's X-Stop Interspinous Process Decompression System in November 2005; Biomet's C2a Taper in December 2005; and Smith & Nephew Orthopedics' Birmingham Hip Resurfacing System in May 2006.

In February 2006, FDA issued a reclassification proposed rule and draft special controls guidance document for the intervertebral body fusion device. Mr. Ogden stated that FDA is drafting guidances for the following areas: mobile bearing knees; metal on metal hip prosthesis; cartilage; the artificial disc; hip joint clinical study; femoral stem; cemented knee joints; and ultra-high molecular weight polyethylene.

Mr. Ogden reported that there is a new CDRH eCopy initiative to facilitate and expedite premarket reviews. It encourages manufacturers to submit an electronic duplicate of premarket submissions in lieu of one required paper copy.

Lastly, the Orthopedic Devices Branch was divided into the Orthopedic Joint Devices and Orthopedic Spine Devices Branches, and Mr. Mark Melkerson is now the Division Director.

OPEN PUBLIC HEARING

The Chairman gave an overview of the day's agenda before the Open Public Hearing. Ms. Scudiero read the open public hearing statement. Two individuals and one group spoke in the morning open public hearing.

Dr. Stephen Gordon, Executive Vice President of Healthtronics, Inc., spoke in favor of reclassification of the non-invasive BGS. Healthtronics believes that the **s**ponsor's proposed guidance document, "Class II Special Controls Guidance Document - Contents of Premarket Notifications for Non-Invasive Bone Growth Stimulators," provides the elements necessary to design a non-invasive BGS device that is substantially equivalent to predicate non-invasive BGS devices, since waveforms and tissue electrical fields that have been shown to be safe and effective are defined in the guidance document. Down-classification of BGS devices also follows the least-burdensome provisions of the FDA Modernization Act of 1997 and would encourage improved commercial access for delivering safe and effective BGS devices.

Dr. Gary Friedlander of Yale University, a former Panel member, spoke in opposition to reclassification of the BGS. Smith & Nephew paid for his travel. He stated that substantial equivalence to existing approved devices was unwarranted, potentially problematic, risky, and not in the best interest of the public. He said that minor changes to a BGS can cause significant changes in biological effects. Because the mechanism of the non-invasive BGS's action is not understood, effectiveness should be demonstrated.

The Bone Growth Stimulator Opposition Group (the BGS Opposition Group) representing DJ Orthopedics, EBI, and Orthofix spoke next. Their representatives were Drs. Barbara Boyan from Emory University and the Georgia Institute of Technology, James Ryaby from Arizona State University, and Neil Khahnovitz from the Center for Orthopedics. They believe the reclassification could result in ineffective and unsafe devices entering the market.

Dr. Boyan said that the petition does not meet the following regulatory requirements for reclassification: a device description with technical specifications; an identified generic device class; valid, published scientific evidence; and proposed special controls. She stated that the two BGS modalities, capacitive coupling (CC) that works via an electronic field directed to the patient via a skin contact electrode, and pulsed electrical field (PEMF) in which fields are delivered via coils, are marketed for different indications and have different biological effects. She believes not enough is known about the devices and the petition does not give sufficient data to reach a conclusion of equivalence.

Dr. Ryaby stated that the petition insufficiently described the devices' technical specifications and tolerances. He said that seemingly minor changes in waveforms could render the devices ineffective or unsafe. He cited the following: his 1994 research; Dr. Brighton's 2006 publication on bone morphogenic protein (BMP) gene expression as a function of frequency that showed that no effect and maximal effect are a matter of very small changes in the signal's magnitude; and Drs. Leisner's and Barker's preclinical animal studies on pulsed magnetic field therapy.

Dr. Khahnovitz, a researcher for EBI, said that reclassification of the generic BGS generic is invalid because fusions in different parts of the body heal differently. He pointed out that the design differences among the published studies make comparisons difficult. He noted small sample sizes, lack of randomized prospective studies, lack of proper control groups, and differences in treatment schedules and clinical and radiographic follow-up among the studies. Although the petitioner had said that the differences helped support the study, Dr. Khahnovitz believes that the differences are actually discrepancies and inadequacies that lead to scientific invalidation.

Dr. Boyan concluded the BGS Opposition Group's presentation by stating that the petition fails to demonstrate that the PMA requirements are unnecessary and that the class II classification assures safety and effectiveness.

RECLASSIFICATION OVERVIEW

Ms. Marjorie G. Shulman of the Office of Device Evaluation briefed the Panel on the reclassification regulations. She explained that the Act divided medical devices into preamendment and postamendment devices, depending on when the devices were introduced into commercial distribution. As a postamendment device, the noninvasive BGS, the subject of this meeting, is automatically a class III device. The device remains in class III and requires premarket approval unless it is reclassified or FDA issues a

substantial equivalence determination. Reclassification of postamendment devices can be initiated by FDA or by industry, and FDA may refer a reclassification petition to a panel for their recommendation.

She stated that a device should be placed in the lowest class with a level of control that will provide reasonable assurance of safety and effectiveness. The three device classes and their respective levels of control are class I (general controls), class II (special controls), and class III (premarket approval).

Class III devices are those for which insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of safety and effectiveness of such device. These devices include implants, are life-sustaining or life-supporting, are of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury.

Class II devices are those that cannot be classified into class I because general controls are insufficient but can be assuredly safe and effective with special controls. Special controls include performance standards, postmarket surveillance, patient registries, development and dissemination of guidance or guidelines, design controls, recommendations and other appropriate actions, tracking requirements.

Class I is for devices for which any combination of the general controls is sufficient to provide reasonable assurance of safety and effectiveness of the devices.

SPONSOR PRESENTATION

Mr. Bill Carroll, Vice President for Research and Development at RS Medical, began by stating that he believes the non-invasive BGS can be regulated as a class II device. Then he introduced the sponsor's presenters: Mr. Robert L. Sheridan, R. Sheridan Consulting, LLC; Cathy S. Carlson, D.V.M., Ph.D., College of Veterinary Medicine, University of Minnesota; Edmund Frank, M.D., F.A.C.S., Oregon Health and Sciences University; Christine Brauer, Ph.D., Brauer Device Consultants; and Jeffrey Skinner, Vice President, Engineering, ControlTek, Inc.

Mr. Robert Sheridan, a former CDRH ODE director, explained device reclassification criteria. There are two sets of criteria for reclassifying devices. Postamendment devices are automatically class III unless they are substantially equivalent to a preamendment type of device. The non-invasive BGS was classified into class III due to differences from the preamendment device. He stated that this class III designation was meant to be temporary unless the device is one that presents an unreasonable risk, one for which general or special controls are insufficient, or one that is of special importance in preventing impairment to health. Mr. Sheridan believes that sufficient special controls for this device can be established.

The petition requests reclassification of a generic type of non-invasive BGS device, defined as a group of devices that do not differ significantly in purpose, design, materials, energy source, function, or any other feature related to safety and effectiveness. The definition does not require that the device's identification include its specifications. The petition describes the technological characteristics related to the device's mode of action and its intended use, i.e. to provide stimulation through electrical and/or magnetic fields to promote osteogenesis to facilitate the healing of nonunion fractures and lumbar spinal fusions. The petitioner believes that the non-invasive BGSs have the same intended use and that differences in the bone being fused do not affect the nature of the risks to health.

Mr. Sheridan stated that FDA has traditionally been flexible about the other conditions of device typing. He cited the example of pedicle screws. If the intended use and risks are the same, FDA tends to group devices together. While non-invasive BGSs may deliver stimulation through CC electrodes or PEMF coils, they have the same intended use and the risks to health; and, therefore, similar regulatory controls can provide reasonable assurance of safety and effectiveness. Mr. Sheridan said that is the case with these devices, that the risks to health and modes of failure can be mitigated by class II controls. Unsafe and ineffective devices can be designed in accordance with the petition's device identification, but the issue is whether these designs can be identified by general or special controls prior to distribution. He noted that a reclassification panel meeting is different from a PMA panel meeting in that a reclassification panel meeting addresses whether or not a PMA is required and whether the devices can be safe and effective if adequately controlled, not the actual safety and effectiveness of a specific particular device.

Dr. Carlson spoke on the device's mechanism of action and testing. Musculo-skeletal tissues respond to biophysical stimulation, including electrical and electro-magnetic fields. Such stimulation regulates the expression of genes in connective tissue cells for structural extracellular matrix proteins to increase in cartilage and bone production. In *in vivo* models and clinical situations, this can be manifested as enhanced repair and/or a gain in mechanical properties of bone.

Dr. Carlson stated that although the two types of devices differ in design, their effects at the cellular level are similar. Both types of signals up-regulate messenger RNA levels for growth factors, increase alkaline phosphatase activity, important for bone cell development and bone matrix mineralization, and increase bone cell proliferation.

In Dr. Brighton's study, inhibitors of signal transduction were used to determine the mechanisms of action of the signal response. Dr. Carlson stated that capacitive and inductive signals both produced a significant increase in cell proliferation compared to controls at all time points examined. She believes that further research will likely identify signals that trigger other actions, as well as help separate ineffective from effective signals, and this is already being done in animal models. While some studies show no effect on bone fracture healing and bone strength, most show positive effects,

and there is no evidence of deleterious effects. Cellular, animal, and clinical tests are all available controls under class II.

Dr. Frank reviewed 43 clinical studies, including 41 peer reviewed articles in which over 6,500 patients were treated and two RS Medical articles. Twenty-nine of these 43 studies were prospective studies. There were over 5600 patients in the 35 nonunion fracture studies and 880 patients in the eight lumbar spinal fusion studies. Dr. Frank concluded from his review of the literature that use of non-invasive BGSs provides safe and effective treatment for patients. Despite the study differences, all but two studies provided evidence of device effectiveness.

Dr. Brauer addressed risks to health and the class II controls to control these risks to health. To remain a class III device, the non-invasive BGS must present an unreasonable risk of illness or injury and there must be insufficient information to determine that general and specific controls will provide assurance of safety and effectiveness.

Seven risks to health associated with use of the non-invasive BGS were identified from the literature, FDA's databases, and estimates of theoretical risks. Four risks to health, i.e., electric shock, burns, skin irritation, and allergic reaction, are rarely serious injuries; they can be controlled by device design, by modifying treatment, or by terminating treatment. Theoretically, the remaining three risks to health could cause a serious injury. These include damage to an implanted electrical device, such as a pacemaker; adverse biological effects of stimulation, such as carcinogenicity; and ineffective or inconsistent treatment, including ineffective treatment due to the presence of a magnetic fixation device. However, these risks to health are not unreasonable because they can be eliminated or mitigated by regulatory controls. In fact, many class II devices have the same risks to health. The sponsor's petition has identified potential causes of each risk to health and has proposed mitigations and regulatory controls for each risk to health.

The sponsor's proposed guidance document identifies testing requirements for the device, and RS Medical has performed the proposed testing on seven commercially available CC devices to demonstrate that such testing can easily be performed for new and existing devices. These testing reports are in the petition.

Mr. Skinner then presented on waveforms. He said that standard engineering design practices allow a manufacturer to design a device that produces the same output waveform within the tolerances of a device whose waveform can be measured. He stated that if the waveform can be measured, it can be reproduced. This results in competition among companies that ultimately benefits the consumer. His company applied well-established techniques to characterize the circuits, systems, and signals of SpinalPak I and SpinalPak II. The spectrum analyses of their output waveforms are not identical, but they share the same fundamental frequency and magnitude.

Dr. Brauer added that RS Medical had also tested the two existing PEMF devices to demonstrate that successful testing could be done. The information from such testing of a new device and a predicate device can be submitted in a 510(k) to demonstrate how the new device is the same as or different from its predicate. This process will ensure that ineffective signals are not marketed.

Mr. Skinner then stated that the sponsor has identified general and special controls to provide a reasonable assurance of device safety and effectiveness based upon the risks to health and their mitigations. These proposed special controls include design controls, the CDRH software testing guidance document, the proposed guidance document for the non-invasive BGS, well-known industry standards for electrical safety, biocompatibility, labeling requirements, and electrode performance standards. The proposed special controls are well-established and have been used for many medical devices. They rely heavily upon recognized standards and upon the fundamental FDA regulatory controls for class II devices, such as design controls and labeling.

Mr. Carroll concluded that the non-invasive BGS does not present an unreasonable risk to health and that general and special controls will provide a reasonable assurance of safety and effectiveness for new devices. Therefore, he believes that it should be reclassified into class II.

The Chairman opened the floor to questions from the Panel. Dr. Sanjiv Naidu asked Dr. Frank how he and Dr. Khahnovitz looked at the same literature and reached such disparate conclusions. Mr. Sheridan responded that Dr. Khahnovitz's study acceptance criteria were designed to ensure failure because he declared any study with fewer than 60 subjects was invalid, randomization was necessary, and one-year outcome data were needed to determine benefit. Mr. Sheridan agreed that information about specific devices was not always provided, and that these were PMA issues, not reclassification questions.

Ms. Pamela Adams asked Dr. Carlson whether enough is known about the animal models to predict effectiveness in humans if a technology change or change in waveform output were to occur or if clinical information would be warranted in that situation. Dr. Carlson said that an animal model would be the first step, but the devices would have to show effectiveness in humans.

Dr. Naidu asked Dr. Khahnovitz the same question he asked Dr. Frank and added the question, if these studies are so bad, how can anyone continue to use the products? Dr. Khahnovitz answered that the six criteria he used are basic meta-analysis criteria that all articles are subjected to. He said that the PMA data is a completely different set of statistics. He added that BGSs, which affect basic physiology, are not comparable to pedicle screws, which are inert objects.

Dr. Stuart Goodman asked the BGS Opposition Group to explain how reclassification to class II might produce unsafe products.

Dr. Kirkpatrick asked two questions. Regarding safety he wanted to know the number of adverse events in the studies, including their severity and type. Second, he asked about the engineering variables for PEMF and CC, what parameters the BGS Opposition Group believed should be defined, and what should be included in a guidance document. He asked RS Medical to prepare responses to the BGS Opposition Group's objections and for his questions.

FDA PRESENTATION

Mr. Michel D. Janda, a GSDB reviewer, gave the FDA presentation. A non-invasive BGS is typically composed of a waveform generator and device accessories. The non-invasive nature of the device does not require sterile components. However, patient-contacting surfaces should be capable of being cleaned, and biocompatibility must be assured. The device utilizes an electrical component to produce an output electrical and/or magnetic waveform that is delivered to a treatment site via non-invasively-applied coils or electrodes. The induced electrical and/or magnetic fields are generated using CC, PEMF, or combined magnetic fields. The indications for this general category device include treatment of an established non-union acquired secondary to trauma, as an adjunct to lumbar spinal fusion surgery at one or two levels, as treatment of congenital pseudoarthrosis, and as an adjunct to cervical fusion surgery in patients at high risk for non-fusion.

Non-invasive BGSs are class III medical devices subject to PMAs. Since 1979, FDA has approved five non-invasive BGS PMAs. FDA has also approved numerous PMA supplements for design, manufacturing, and labeling modifications.

RS Medical is petitioning FDA to reclassify the non-invasive BGS from class III into class II. The FDA seeks the Panel's recommendation on whether sufficient scientific knowledge exists to adequately identify the risks to health associated with the proposed generic device type and if the proposed special control (the sponsor's draft guidance document) is sufficient to control these risks to health. The RS Medical reclassification petition includes five PMA-approved devices and the petitioner's new device (not cleared now). RS Medical's petition includes the following indications for use: treatment of an established non-union acquired secondary to trauma and as an adjunct to lumbar spinal fusion surgery at one or two levels. The indications for treatment of congenital pseudoarthrosis, and as an adjunct to cervical fusion surgery in patients at high risk for non-fusion are not included. Also not included are combined magnetic fields devices, the invasive BGSs and the ultrasound non-invasive BGS.

Since 1984, 46 adverse events were reported for this device in FDA's MAUDE and MDR databases. There were 14 malfunctions, 30 serious injuries, and 2 deaths. The deaths both involved an implanted cardiac device; it is unclear whether or not there was a device interaction. Burns were the most common adverse event with 13 events. These occurred most frequently when the device was being used during recharging of the battery.

The sponsor identified the following seven risks to health: electrical shock, thermal burn, skin irritation and/or allergic reaction, inconsistent or ineffective treatment, adverse interaction with electrical implants, adverse interaction with internal/external orthopedic fixation devices, and biologic effects. To mitigate these risks to health, the sponsors proposed the use of a special controls guidance document that addresses device performance testing, labeling, and biocompatibility.

RS Medical's proposed draft guidance document that incorporates FDA-recognized performance standards and existing FDA guidance documents as special controls. Their draft guidance document includes the following sections: introductory, background, and abbreviated 510(k) information; the scope of guidance document; a description of the device; risks to health; a guide to preclinical analysis and testing; biocompatibility; electronic equipment safety; electromagnetic compatibility; software life cycle and risk management; animal testing; clinical testing; and labeling. If FDA reclassifies the device, the agency will create the final guidance document.

Mr. Janda commented that a reasonable assurance of safety and effectiveness has been demonstrated for the five FDA-approved non-invasive BGS devices. The cited, scientific literature indicates that although some treatment signal field modifications can affect the device's safety and effectiveness, most modifications within a given range do not result in an unsafe or ineffective treatment. The issue raised by the reclassification is whether sufficient scientific knowledge exists to adequately identify the risks to health associated with the proposed generic device type and if the proposed special controls are sufficient to control these risks to health. In assessing the risk profile for any device, it is not possible to prove that a particular adverse event will not occur. Therefore, the proposed special controls should be evaluated to determine if they can control, not eliminate, such risks to health.

The Chairman asked for the number of BGS devices in use to compare to the number of adverse events. Mr. Janda replied that the number of marketed devices is not reported as part of the adverse event databases. Dr. Goodman asked about the three cases of tumor/lesion and two cases of blisters resulting in below-the-knee amputations.

PANEL DELIBERATIONS

Two Panel members who had prepared remarks opened the panel's deliberations. Dr. Jay Mabrey commented on the clinical use of device. He said that BGSs may influence the production of BMPs, which may influence fracture healing. The process is highly sensitive to frequency, field strength, and duty cycle and that the non-invasive BGS include CC, PEMF, and combined magnetic field devices. CC devices use small skin pads or electrodes that are placed on either side of the fusion site. They are worn for up to 24 hours a day until healing occurs or for up to nine months. PEMF devices are delivered via external copper treatment coils placed into a back brace or directly on the skin, and they are worn for six to eight hours per day for three to six months. Combined magnetic field devices superimpose a time-varying magnetic field onto a static field. These are used for a half hour at a time over nine months and deliver 2 percent of the

energy of a PEMF device. Randomized studies of both CC and PEMF devices suggest that they are effective for the indicated uses.

Dr. Cedric Walker addressed the engineering aspects of the devices, starting with the possible adverse events associated with their use: burns and interactions with pre-existing implanted metallic devices. All of the reported burns were associated with the battery-charging circuit on the device, which good engineering can control. A metallic implant can reduce the effectiveness of the BGS device; in particular pacemakers or implanted defibrillators can harmfully interact with the device. One way to mitigate this type of interaction is to use the device far from any pacemaker or defibrillator. Because PEMF devices operate at a frequency that is a sub-harmonic of the normal cardiac rhythm, it should be contraindicated for patients with implantable defibrillators.

Dr. Walker researched the class of other electro-stimulator therapeutic devices. The three devices he found were all preamendment devices that operate at higher current levels than the BGS. All have variable waveforms that are ineffective and harmful if not properly set. The BGS devices proposed for reclassification all create frequencies and fields that are below the thresholds generally acceptable for interactions between electromagnetic fields and humans. There is no Federal standard for allowable electric or magnetic fields, but some states have standards. Florida has the strictest at 2000 volts per meter. The BGSs operate far below this threshold. The BGSs expose patients to about 18 milligauss, which is less than the exposure from sewing machine. The exposures from the devices are all very low, and the only danger to humans would be if the frequency were to be too low, which could cause muscle activation, perception, pain, and other effects. He believes that there is little danger to humans at the level proposed.

The Chairman invited the Consumer Representative to comment. Ms. Connie Whittington said that she has utilized the devices for a long time and has seen no adverse events. She emphasized the need for education and information not only in the professional literature but also in the patient education literature.

Ms. Adams, the Industry Representative, commented that RS Medical faces an unusual burden, since down-classifications are usually sponsored collaboratively by an entire industry rather than a single company. Without this sort of collaboration, they have not had access to resources and proprietary information from other companies. This does not affect how safe or effective the devices are, but it does affect the amount of information submitted.

GENERAL PANEL DISCUSSION

The Chairman gave each Panel member an opportunity to comment. Dr. Kathleen Propert said that the small size of the studies and their lack of randomness concerned her, and there might not be enough data. Dr. Roger Nelson was concerned about outcomes reporting and the lack of quality of life data. Dr. Leon Lenchik said that non-standardized radiologic endpoints are a concern. Radiologic measures of healing are not as important as clinical measures, but any measure used should be defined. Dr. Goodman

commented on the disparity of analysis between the sponsor and opposition, and he wanted to hear more about safety. Dr. Naidu said his major concern was that there was inadequate data on clinical efficacy. He stated that the existing clinical evidence is poor and the fracture cases are very old data. Dr. Mabrey commented that BGS are essentially BMP dosing devices that may or may not work. The effects of these waveforms and of BMP are not fully understood. He also indicated that the literature is spotty. Dr. Choll Kim asked about the design differences of existing devices and how they affect waveform dosing and how they can all work if they are so different. He also wanted to know if the pre-clinical data predicts efficacy. Mr. Mark Melkerson commented for the FDA that PMA supplements changing the frequency should require a new clinical data.

Dr. Simon of the BGS Opposition Group said that he had had a successful pre-clinical trial on a device that turned out to be unsuccessful in clinical trials. The pre-clinical data in these studies have been published. He concluded that animal and cell models are not always predictive. The Opposition Group commented that although the signals are different, there are 12 parameters that remain the same throughout the PMA supplements. Mr. Sheridan, for the sponsor, said that they had found no case of a pre-clinical trial that did not predict the clinical outcomes.

The Chairman asked the Panel whether it is concerned that although the electrical output of the device is known, it is not known what output reaches the different tissue depths. Ms. Whittington pointed out the variation in tissue depth between emaciated and obese patients. Dr. Walker said that a specific electrical field endpoint can be maintained by adjusting output for the distance between the electrodes. When coils are used, getting to the right output is a matter of clinical judgment. Dr. Simon from the PMA Opposition Group said that the conductivity of tissue does affect the fields, and in obese patients, the electrodes can be too far apart. The distance between the electrodes is important. In his trials, the position of the electrodes on the patients and the power setting were both fixed; the electrodes were placed across the fracture, making no allowance for patient size. The results were not as high as they could have been, had the optimal position been calculated, but there was still 85 percent success in the test group, compared to 65 in the control. He pointed out that the PEMF signal is 18 Gauss, not milligauss, so it is nearly three orders of magnitude higher than the Florida standard. The duty cycle is around 7 percent.

Ms. Whittington pointed out that the patients using the devices are likely to have concurrent diseases and comorbidities.

The Chairman asked the Opposition Group to address the package inserts. Dr. Simon said that some contraindications in the inserts, such as pregnancy, are not based trial data, but are included for safety. The pacemaker warning is due to interactions in a dog model.

Dr. Naidu asked Dr. Walker to address safety. Dr. Walker said that the field strengths and current voltages are far sub-threshold and very safe. Mr. Carroll of RS said that Table 1 came from a review paper from Dr. Nelson, but it was presented in the

wrong context. Dr. Walker said that even without exact numbers, the strengths and voltages are clearly at a safe range. Mr. Sheridan said that the actual device performance parameters are 510(k) review issues. The Chairman agreed that it is technically true, but the Panel may need to know about the signals in order to recommend effective special controls.

The Chairman then followed up on the questions asked before lunch. He started with the number of adverse events in the published literature. Dr. Khahnovitz of the Opposition Group said that there are not many adverse events in the literature. Dr. Brauer (for the sponsor) provided a summary of the safety data that appears in the petition. Dr. Brauer said that that was out of 41 articles reviewed.

The Chairman then asked that both groups identify the 12 variables for PEMF and the 4 variables for CC. Dr. Simon of the Opposition said that five parameters for PEMF are burst frequency: pulse on and pulse off durations, the number of pulses per burst, burst length, and peak amplitude. The other seven parameters are proprietary, but they have to do with the shape of the pulse waveform. They appear in the PMA data and include such things as curve shape, frequency distribution, and attenuation. Mr. Melkerson said that the FDA uses a set of characteristics for all sponsors, based on the descriptive characteristics used in the PMA. Ms. Adams asked about the guidance document and the signal characteristics it lists. Mr. Melkerson said that signal characteristics could be used for comparisons to a predicate product. Dr. Walker said that the definitions are very effective, and several different devices can be evaluated using a general set of characteristic parameters.

For the FDA, Dr. Aron Yustein then reported on the MDRs. The two blister cases that resulted in below-the-knee amputation were duplicate reports for the same patient, a 62-year-old diabetic male. The blister was on his foot; the report does not indicate where the device was applied. Of the three tumor lesion reports, one was a duplicate. One was a 58-year-old male using the device eight hours per day for three months. After a lobectomy, it was determined that the lesion was actually benign calcification. The other case does not have details.

The Chairman asked if there were any further questions. Hearing none, he moved on to the FDA Panel questions.

FDA QUESTIONS

The Chairman read each question to the Panel and asked each Panel member to respond to the questions. He then summarized the Panel's responses to the questions as follows:

Question 1: In regards to the following devices which are proposed for reclassification, do you believe that the device description adequately describes and characterizes the devices? If not, what changes in the definitions or

characterizations do you recommend? The Panel agreed that both the CC and PEMF devices were adequately described and characterized.

Question 2: In regards to the following devices which are proposed for reclassification, do you believe that the risks to health are adequately described? If not, what additional risks do you believe should be included for a) CC and b) PEMF devices? The Panel believed that the identified risks to health for both CC and PEMF devices were adequately described and complete.

Question 3: Special controls have been proposed to address the risks to health identified for each of the above device configurations. Do you believe appropriate special controls have been identified to adequately address these risks? If not what additional controls would you recommend?" Five members believed that proposed special controls were inadequate for various reasons, including uncertainty about guidance documents, inadequate treatment is a risk to health, and a lack of randomized, controlled studies. Some thought a new clinical study was needed. Three members believe the proposed controls were adequate; one because of 30 years experience with the device.

The Chairman asked the five members who believed that the proposed special controls were inadequate if removing non-effective or inadequate healing from the list of risks to health would change their vote. Three of the five stated it would and one said possibly.

Question 4: Device labeling has been cited as a control with which to address risks to health. The proposed labeling requirements are consistent with those generally found in current non-invasive BGS package labeling. This labeling generally includes device description, type of material, indication for use, contraindications, adverse events, precautions, warnings, a listing of compatible components, and sterility information. What additional labeling, if any, do you recommend for the CC and PEMF devices? The Panel unanimously said that the labeling was adequate. The Chairman said that co-morbidity and obesity issues are labeling indications for use/ contraindications issues.

Question 5: Do you believe the data presented in this petition supports reclassification of: a) all non-invasive capacitive coupling BGS devices as identified in this petition? If not, which types do you believe are inappropriate for reclassification and why? b) all non-invasive Pulsed Electromagnetic Fields capacitive coupling BGS devices as identified in this petition? If not, which types do you believe are inappropriate for reclassification and why? Most of the Panel believe the data in the petition supports reclassification of both CC and PEMF devices; one member believes the data did not support reclassification of both devices.

The next three questions were categorized as general questions.

Question 6: The proposed reclassification excludes the combined magnetic fields device. Please discuss if the risks associated with this device are significantly different than those risks to health associated with the proposed general device type. The Panel except for the two members who abstained believed that risks to health were the same and the devices should be classified together.

Question 7: The proposed reclassification excludes the invasive BGSs and the non-invasive ultrasound BGSs. Please discuss if the risks associated with these product types are significantly different than those risks to health associated with the proposed general device type." The Panel indicated that a combined magnetic fields device may be included as long as it seems to be of reasonable similarity. The Panel agreed that implanted devices have additional risks to health that non-invasive devices do not have. The Panel didn't have specific comments on the ultrasound device.

Question 8: The proposed reclassification excludes indications for the treatment of congenital pseudoarthrosis and as an adjunct to cervical fusion surgery in patients of high risk for non-union. Please discuss if the risks associated with these indications for use are significantly different than those risks associated with the proposed general device indications for use. The Panel unanimously said that there was insufficient data to make a decision about pseudoarthrosis.

OPEN PUBLIC HEARING

Dr. William Beutler of the Pennsylvania Spine Institute was the first presenter of the second open public hearing. He has no financial connection with any of the companies, but he does use Orthofix and EBI's BGS and RS's sequential stimulators in his practice. He said that failed fusions have the serious complication of morbidity, and that he uses BGS to prevent failure in higher-risk patients. He does not know how the devices work, but he finds that there often is a benefit. However, ineffectiveness is a serious complication, and since no one knows how the device works, the only way to know a device will work is through PMA trials. Ineffective devices will lead to failed fusions and morbidity.

Dr. Roy Aaron, a consultant to EBI, said that the clinical use of ineffective signals will deny other therapy, increase morbidity, is unethical, and should not be allowed in the marketplace. All physical signals have an anabolic and catabolic effect on bone, and they all have dosimetry. However, that dosimetry is expressed in a manner that is very complicated and poorly understood. In this sense, there is no such thing as a generic device. From multiple studies from different laboratories, he has concluded that it is possible to create biologically ineffective signals, and their clinical use will deny more effective treatment. It is difficult to translate preclinical data to clinical use, so prospective clinical trials are needed.

Dr. Aaron read a letter from Dr. Joseph Lane of Cornell. Dr. Lane urged the Panel to not reclassify BGS devices due to the lack of studies and information about these

devices. He feared that reclassification would let unproven and potentially ineffective devices into the market.

Dr. Khahnovitz for the BGS Opposition Group reiterated their earlier presentation, emphasizing the potential of approving generic devices that may not be effective. The studies on these devices are often old and do not stand up to current criteria. The danger to the patient of the use of an ineffective device would be significant.

Dr. Aaron read a letter from Dr. Thomas Einhorn of the Boston Medical Center into the record. Dr. Einhorn urged the Panel to deny the reclassification request. He believes that the studies have been insufficient and that there is no basis to conclude that a BGS is effective without a proper clinical trial. To reclassify would allow unproven and ineffective devices into the market and put patients at risk.

Dr. Ronald Midura of the Cleveland Clinic Lerner College of Medicine presented for Orthofix. He stated that little is known about BGSs, and similar devices can have different results. In his research, he found that an ineffective signal can be produced that itt not statistically different from an effective signal. The ineffective device was produced by the same manufacturer as the effective device, and it used the same technologies. The ineffective healing may actually have delayed the normal healing process. Research to develop a scientific understanding of biological reactions may someday make it possible to predict clinical results in advance. However, the science is not yet there. He finished his presentation with time yielded him by Ms. Fellows of Orthofix.

Ms. Fellows yielded time to Dr. Jim Ryaby, who summarized his earlier remarks that it is impossible to show substantial equivalence on a device that you do not understand. He advocated clinical trials and said that class II does not provide a rigorous assessment. Therefore, he said that the devices should remain class III devices.

Ms. Fellows yielded the remainder of her time to Dr. Simon who reiterated that the effects of even minor deviations in signal are unknown. Without a scientific understanding of what the parameters should be, there can be no generic class of devices.

John Roberts presented on behalf of the Orthopedic Surgical Manufacturers Association, OSMA. He urged the Panel to focus on product safety and effectiveness. He emphasized two points: responsible assurance of safety and effectiveness and valid scientific evidence. He asked the board to consider carefully, to remember that the standard is a balance between benefits and risks, and to not unnecessarily delay any useful product.

FDA SUMMATION

Mr. Melkerson said that the FDA had nothing to add. However, he asked if he was correct in understanding the BGS Opposition Group's position that any change to an

existing wave signal, in energy or waveform, would require randomized, clinical trials for approval. Dr. Khahnovitz said that was correct.

SPONSOR SUMMATION

Mr. Sheridan spoke for RS Medical. He suggested that the physicians who spoke and wrote in did not really care about device classification as long as the device is safe, effective, and based on good science. He disagreed with presenters who said that the waveforms on new BGSs will be unknown. They will be characterized in every way a waveform can be characterized, and exact waveforms can be duplicated. He said that the 510(k) process is an effective process.

He said that RS Medical has described a device type that meets the requirements. Specifications are not part of the device identifications because this is "a 510(k) review matter handled" when substantial equivalence is determined. RS Medical provided a rationale for reclassification, showed safety and efficacy, and identified the risks to health associated with the device. RS Medical has proposed special controls that would make the device safe under class II.

He rebutted the BGS Opposition's allegations about a lack of scientific evidence, quoting the definition of scientific evidence and pointing to the studies that were referenced. The data in the scientific literature and in the petition demonstrate that the device can be safe and effective. He also stressed that the data in the petition were identical to the data in PMA submissions.

He reviewed the class II controls for the mitigation of risks. The main issues of reclassification is avoiding ineffective signals and ensuring proper manufacturing. The 510(k) guidance will take care of that, and it will dictate testing if necessary. There is no difference in quality system regulation requirements between class II and class III devices. The FDA will still review the device's design and performance and its manufacturing.

GENERAL DEVICE CLASSIFICATION QUESTIONAIRE

Ms. Shulman assisted in the Panel's completion of the reclassification questionnaire. A copy of this is attached.

Question 1 was a unanimous no.
Question 2 was a unanimous yes.
Question 3 was a unanimous no.
Question 4 was yes leading to Question 6
Question 6 was a tie. The Chairman cast the tiebreaking vote to answer yes. The vote was four to three to answer yes.
Question 7 upon discussion, the Panel asked for clarification on the definition and scope of special controls in relation to the type of study they thought was necessary in addition to a guidance document. The Chairman stated that the extensive clinical data

the Panel wanted may be beyond the scope of special controls, since it was complex, dependent on special populations, dependent on specific devices, and the specific outcomes needed to be addressed. Therefore, he returned to Question 6.

Question 6, revisited, was no (vote of four to two). This vote resulted in the Panel's recommendation to retain the non-invasive BGS in class III. The Chairman asked for a motion to accept the Panel's findings as stated. The Panel voted four to two in favor of recommending that the device be retained in class III.

The Chairman asked the Panel members to explain the reasons for their votes. Dr. Walker said that the 510(k) review, FDA review, and inclusion of possible clinical studies in the guidance document would be sufficient safeguards. Dr. Propert said that more studies will be needed before it is possible to define a generic device. Dr. Nelson concurred with Dr. Walker. Dr. Naidu said that there is inadequate clinical data and the available literature is poor. Dr. Mabrey said that device output can not be equated to device effectiveness and the risk of an ineffective device would be hazardous to patients. Dr. Kim said that the key question was whether or not a new device could be compared with a predicate device. With the complexity of the healing and fusion process, he did not believe that parameters of comparison could be established. Until standards of comparison are developed, a PMA should be required.

Mr. Melkerson asked for the Consumer and Industry Representatives' opinions. Ms. Adams expressed regret over the Panel's decision, noting the large effort required to prepare a PMA by a sponsor and the amount of work for the FDA to review a PMA submission. Ms. Whittington said that she felt the need for clinical studies, so she was pleased with the Panel's recommendation.

ADJOURNMENT

The Chairman thanked the Panel, staff, and participants for their work and their participation in democratic, participatory government. He closed the meeting at 3:40 p.m.

I certify that I attended this meeting of the Orthopedic and Rehabilitation Devices Advisory Panel Meeting on June 2, 2006, and that these minutes accurately reflect what transpired.

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Janet L. Scudiero
Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

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John S. Kirkpatrick, M.D.
Chairperson