UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

+ + +

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

+ + +

ORTHOPAEDIC AND REHABILITATION DEVICES PANEL

+ + +

September 8, 2020
8:00 a.m.

Via Webcast

PANEL MEMBERS:

HARVEY E. SMITH, M.D.	Panel Chair
MAUREEN A. FINNEGAN, M.D.	Voting Member
LYNDA J-S YANG, M.D., Ph.D.	Voting Member
JEREMY L. GILBERT, Ph.D.	Voting Member
CARL N. GRAF, M.D.	Temporary Non-Voting Member
KARLA V. BALLMAN, Ph.D.	Temporary Non-Voting Member
DIRK H. ALANDER, M.D.	Temporary Non-Voting Member
BENJAMIN ELDER, M.D., Ph.D.	Temporary Non-Voting Member
GLENN B. PFEFFER, M.D.	Temporary Non-Voting Member
EDWARD EBRAMZADEH ABRAMS, Ph.D.	Temporary Non-Voting Member
COL PATRICK M. OSBORN, M.D.	Temporary Non-Voting Member
STACEY BONNELL, M.B.A., RAC	Industry Representative
JOSEPH P. O'BRIEN, M.B.A.	Patient Representative
AMY PRICE, D.PHIL.	Consumer Representative
JAMES SWINK	Designated Federal Officer

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

FDA REPRESENTATIVES:

CAPT RAQUEL PEAT, Ph.D., M.P.H., USPHS
Director, OHT6: Office of Orthopedic Devices
Office of Product Evaluation and Quality

CONSTANCE SOVES, Ph.D.
Regulatory Advisor, Immediate Office
Office of Product Evaluation and Quality

LCDR RANDOSHIA MILLER, M.S., BSN, RN
Regulatory Health Project Manager
OHT6: Office of Orthopedic Devices
Office of Product Evaluation and Quality

FDA PRESENTERS:

BRITTANY FERRELL, B.S.
Lead Reviewer, Extracolumnar Spinal Devices Team
DHT6B: Division of Spinal Devices
OHT6: Office of Orthopedic Devices
Office of Product Evaluation and Quality

CAROLINE MOAZZAM, M.D.
Medical Officer, Extracolumnar Spinal Devices Team
DHT6B: Division of Spinal Devices
OHT6: Office of Orthopedic Devices
Office of Product Evaluation and Quality

SHUMAYA ALI, M.P.H.
Assistant Director, Stereotaxic, Bone Growth Stimulators, and Fracture Fixations Devices Team
Division of Restorative, Repair, and Trauma Devices
OHT6: Office of Orthopedic Devices
Office of Product Evaluation and Quality

PHILIP BELMONT, M.D.
Medical Officer, Knee Arthroplasty Team
Division of Joint Arthroplasty Devices
OHT6: Office of Orthopedic Devices
Office of Product Evaluation and Quality

JESSE MUIR, Ph.D.
Lead Reviewer, Stereotaxic, Bone Growth Stimulators, and Fracture Fixations Devices Team
Division of Restorative, Repair, and Trauma Devices
OHT6: Office of Orthopedic Devices
Office of Product Evaluation and Quality

OPEN PUBLIC HEARING SPEAKERS:

MEG SEYMOUR, Ph.D.
Senior Fellow
National Center for Health Research

WILLIAM C. WELCH, M.D.
University of Pennsylvania

CHARLES SANSUR, M.D.
Director, Spine Surgery
Department of Neurosurgery
University of Maryland School Medicine
On behalf of the AANS and CNS

ROBERT MURATORE, Ph.D.
Chief Scientific Officer
Acoustic Sciences Associates LLC

JAMES T. RYABY, Ph.D.
Chief Scientific Advisor
Orthofix Medical
On behalf of the Bone Growth Stimulator Coalition

MOHIT BHANDARI, M.D., Ph.D., FRCSC
Professor/Academic Head, Orthopaedic Surgery
McMaster University
On behalf of the Bone Growth Stimulator Coalition

CHI LIM, M.D.
Orthopaedic Spine Specialist
On behalf of the Bone Growth Stimulator Coalition

INDEX

INDEX

INDEX

M E E T I N G

(8:00 a.m.)

DR. SMITH: I would like to call the FDA's Center for Devices and Radiological Health Orthopaedic and Rehabilitation Devices Panel for the Medical Devices Advisory Committee on September 8th, 2020, to order. It is now 8:00 a.m.

I'm Dr. Harvey Smith, the Chair of this Panel. I'm Associate Professor of Orthopaedic Surgery at the University of Pennsylvania.

I would like to introduce Captain Raquel Peat, Director of OHT6: Office of Orthopedic Devices in the Office of Product Evaluation and Quality at FDA, who has some introductory remarks for the Panel.

Captain Peat, you may proceed.

DR. PEAT: Good morning to all and welcome to the Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee meeting.

My name is Captain Raquel Peat and I am the director for the Office of Health Technology 6: Office of Orthopedic Devices within the Office of Product Evaluation and Quality here at CDRH.

I am really excited to have all of you participating in today's event. This is a unique period in our history as we respond as a nation to the COVID-19 pandemic with the first virtual panel meeting of this type within our office.

Additionally, there are a number of participants that further emphasizes the importance and interest in having our September 8th and 9th, 2020 Orthopaedic and Rehabilitation Devices Panel meeting. Of the many who are participating in this panel meeting, I want to extend special thanks to our Advisory Committee staff, specifically James Swink and Commander Patricio Garcia and Lieutenant Commander Randoshia Miller, Regulatory Health Project Manager, who have been instrumental in leading this panel

meeting; staff and managers in the Office of Health Technology 4 and 6 and other areas of FDA that includes the FDA studio staff, presenters, and our esteemed panelists who are contributing to the implementation of a successful panel meeting. And of course, you, our participants.

The objective of our panel meeting is as follows: As required by Section 513(b) of the Federal Food, Drug, and Cosmetic Act, the Food and Drug Administration is convening the Orthopaedic and Rehabilitation Devices Panel for the purposes of obtaining recommendations about the classification and reclassification of identified orthopedic medical devices. FDA is holding this panel meeting to obtain input from the Panel to provide input on the appropriate classification, as well as ensuing discussion on the available scientific evidence that includes dialoguing on the appropriate controls necessary to mitigate the risks to health and assure the safety and effectiveness of these devices.

As such, we will discuss the reclassification of noninvasive bone growth stimulator devices and four preamendments on classified medical devices, notably facet screw systems, semi-constraint toe joint prostheses, intracompartmental pressure monitor devices, and intra-abdominal pressure monitor devices.

I wanted to highlight that the general public can submit either electronic or written comments on the proposed order for the reclassification of noninvasive bone growth stimulators to the docket on the *Federal Register* by October 16th, 2020. I have noted the docket number on the slide for ease of reference. Intermittently, and as a gentle reminder, FDA's studio will repost information on how to submit comments to the docket on your screen each day.

In closing, I wanted to thank all of the panelists and contributors to our 2-day panel meeting. We look forward to having productive and informative discussions over the next couple of days.

I will now turn it back over to our Panel Chair, Dr. Harvey Smith. Thank you.

DR. SMITH: Thank you, Dr. Peat. Captain Peat.

I note for the record that the Panel members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel participating in the meeting today has received training in FDA device law and regulations.

For today's agenda, the Committee will discuss and make recommendations regarding the classification of facet screw systems, which are currently unclassified preamendments devices, to Class II general and special controls.

During Session 2, the Committee will discuss and make recommendations regarding the reclassification of noninvasive bone growth stimulators, which are currently post-amendment devices, from Class III (general controls and premarket approval) to Class II (general and special controls).

I wanted to lay down a few ground rules. If a panelist wants to ask a question, please use the hand-raising function on your Zoom platform and I will get to your questions as we proceed throughout the day. We want to prevent multiple persons from speaking over each other as we proceed, as this entire meeting is being transcribed for the official record.

Before we begin, I would like to ask our distinguished Panel members and FDA attending virtually to introduce themselves. I will call your name, please state your area of expertise, your position, and affiliation.

Captain Raquel Peat.

DR. PEAT: Good morning, everyone. I'm Captain Raquel Peat, Director for the Office of Health Technology 6, the Office of Orthopedic Devices within the Office of Product Evaluation and Quality here in the Center for Devices and Radiological Health. Thank you all for being here today.

DR. SMITH: Stacey Bonnell, our Industry Representative on the Panel.

MS. BONNELL: Hello, good morning. My name is Stacey Bonnell, I'm serving the Panel today as the appointed non-voting Industry Representative. I am employed full time by DePuy Synthes, a company of Johnson & Johnson, where I am the director of the regulatory affairs, and that will be my expertise for today. Thank you for having me.

DR. SMITH: Amy Price, M.S., M.P.H., M.A. (sic), our Consumer Representative on the Panel.

DR. PRICE: Hi, I'm Amy Price and I am a senior research scientist at Stanford University School of Medicine and my specialization is in research methods and in public and community and patient involvement.

DR. SMITH: Joseph O'Brien, our Patient Representative on the Panel.

MR. O'BRIEN: Hi, my name is Joe O'Brien, as Dr. Smith says. I am the president and CEO of the National Scoliosis Foundation. I am also a six-time scoliosis fusion patient.

DR. SMITH: Maureen Finnegan, M.D.

DR. FINNEGAN: I am an associate professor at UT Southwestern and have spent most of my career at Parkland doing sports and trauma.

DR. SMITH: Carla Ballman, Ph.D.

DR. BALLMAN: I'm Carla Ballman, I'm at Weill Cornell Medicine in New York City. I am a Professor and Division Chief of Biostatistics, and my expertise is in biostatistics and epidemiology.

DR. SMITH: Patrick Osborn, M.D.

(No response.)

DR. SMITH: Lynda Yang, M.D., Ph.D.

DR. YANG: Good morning, I'm Lynda Yang. I am a Professor of Neurosurgery at the University of Michigan, specializing in spine and peripheral nerves.

DR. SMITH: Jeremy Gilbert, M.D (sic).

DR. GILBERT: Hi, I'm Jeremy Gilbert, Professor of Bioengineering and the Hansjörg Wyss Endowed Chair for Regenerative Medicine. I am editor-in-chief of the *Journal of Biomedical Materials Research Part B* and my research is in biomaterials.

DR. SMITH: Dirk Alander, M.D.

DR. ALANDER: Good morning. I'm a professor at Geisinger School of Medicine, the Geisinger Commonwealth School of Medicine, and chief of quality at Geisinger Musculoskeletal Institute in Danville.

DR. SMITH: Benjamin Elder, M.D., Ph.D.

DR. ELDER: Hi, I'm Ben Elder. I'm an Associate Professor of Neurosurgery, Orthopedics, and Biomedical Engineering at Mayo Clinic in Rochester, Minnesota. My expertise is in spine surgery as well as bone and cartilage tissue engineering.

DR. SMITH: Carl Graf, M.D.

DR. GRAF: Good morning, my name is Carl Graf. I'm an orthopedic spinal surgeon at the Illinois Spine Institute and my expertise is in spine surgery.

DR. SMITH: Glenn Pfeffer, M.D.

DR. PFEFFER: Can you hear me all right?

DR. SMITH: Yes.

DR. PFEFFER: I'm starting my video, there we are. Okay. Hi, good morning. I'll get a better spot here. Glenn Pfeffer -- I'm in Los Angeles where it's just after 5:00 a.m. -- orthopedic surgeon. I specialize in foot and ankle. I'm director of the foot and ankle center at Cedars-Sinai Medical Center, associate professor.

DR. SMITH: Edward Abrams (sic), Ph.D.

(No response.)

DR. SMITH: James Swink, the Designated Federal Officer for this meeting, will make

some introductory remarks.

MR. SWINK: Good morning. I will now read the Conflict of Interest Statement.

The Food and Drug Administration is convening today's meeting of the Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information of the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses and minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, during Session 1 the Panel will discuss and make recommendations regarding the classification of facet screw systems, which are currently unclassified

preamendment devices, to Class II (general and special controls). During Session 2 the Panel will discuss and make recommendations regarding the reclassification of noninvasive bone growth stimulators, which are currently post-amendment devices, from Class III (general controls and premarket approval) to Class II (general and special controls).

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208.

Stacey Bonnell is serving as the Industry Representative, acting on behalf of all related industry. She is employed by DePuy Synthes, which is part of Johnson & Johnson Medical Device Companies.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which the FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Panel of any financial relationships they may have with any firms at issue.

A copy of this statement will be available for review at the registration table during this meeting and will be included as a part of the official transcript.

Before I turn the meeting back over to Dr. Smith, I would like to make a few general announcements.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Also, the transcripts of today's meeting will be available from Free State Court Reporting, Incorporated.

Thank you very much.

DR. SMITH: We will now proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel, to present data, information or views relevant to the meeting agenda.

Mr. Swink will now read the Open Public Hearing Disclosure Process Statement.

MR. SWINK: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency during this Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationships that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Thank you.

DR. SMITH: There have been two formal requests to address the Panel.

Ms. Meg Seymour from National Center for Health Research, you have 5 minutes.

DR. SEYMOUR: Good morning. Thank you for the opportunity to speak today on behalf of the National Center for Health Research. I'm Dr. Meg Seymour, a senior fellow at the center. Our center analyzes scientific and medical data to provide objective health information to patients, health professionals, and policymakers. We do not accept funding from drug or medical device companies, so I have no conflicts of interest.

Today and tomorrow, the Medical Device Advisory Committee will discuss the proposed reclassification of five medical devices. In particular, you will be asked whether the risks are properly identified and whether the proposed special controls adequately mitigate these risks.

As you know, there have been many concerns expressed in medical journals in recent years about the lack of solid scientific data for medical devices, especially compared to prescription drugs. Our center's staff has spoken for and in opposition, and we've published articles pointing out the lack of definitive information about safety or effectiveness that are made available in premarket applications and 510(k) applications.

Although premarket applications are supported by clinical trials, many fail to include sufficient numbers of people of color, people over 65, and draw conclusions about the benefits of those devices for those important populations.

This meeting is unusual for us, however, because of the lack of information made available to the public prior to this meeting. If the information available to the public is similar to what was made available to members of the Committee, as is usually the case for Advisory Committee meetings, the concern is the Committee does not have sufficient data necessary to adequately evaluate the most appropriate classification for any of these devices.

For example, the Executive Summaries provided by the FDA give little detail regarding the studies done on these devices. It is hard to determine if these studies were well designed, implanted poorly, included sufficient numbers of patients, and were adequately evaluated with meaningful clinical -- clinical endpoints of harm, and there's no information about whether patients of color were included, patients over 65 or other vulnerable groups.

Although there have been recalls in the MAUDE reports, details are often lacking

about the latter. Even when the details are available, as the FDA mentions in the Executive Summary of bone growth stimulators, the prevalence of a risk cannot be determined from a reporting system alone whose adverse events are underreported. So even when risks have been identified, the frequency of those adverse events is not established.

In summary, the Executive Summaries do not provide adequate information for determining whether safety or effectiveness could be ensured without a PMA for any of these devices. If they are classified as Class II, it is unlikely that better data will be forthcoming -- published research has found that the 510(k) process almost never requires evidence of safety or effectiveness.

Today and tomorrow, you're asked to discuss whether the identified risks may be properly mitigated by the proposed special controls over the information that FDA provided to the public, which is supposed to be the same information provided to you as committee members, does not have to describe how frequently the identified adverse events are likely to take place. We respectfully urge you to let the FDA know that Advisory Committee members need more informative scientific evidence of risks and benefits before deciding a classification of a device, and clinical trials are needed if the data are not sufficient to provide information about whether the benefits outweigh the risks.

Further, labeling has been proposed for special controls for many of these devices. For example, one of the proposed additions to labeling is a detailed summary of the clinical testing for the device, as well as the adverse events and complications that occurred with the device. That would provide useful information if the clinical testing is scientifically sound, but only if the label is carefully read. In many cases patients never have devices, especially when he's in surgery, both of who may or may not read or understand all the information included in the label and even if they get a copy of the label, it is almost definitely after the device has been implanted or used in a patient's body. Labels should

provide clear, unbiased information about the risks and benefits of medical products, including all devices. But an original label is not sufficient to provide informed consent. The information that the physician provides to the patient will often be the only information the patients rely on. Unless information is provided by devices -- not just by labels, that is not sufficient as a special control.

Thank you.

DR. SMITH: William C. Welch, M.D., from the University of Pennsylvania.

DR. WELCH: Dr. Smith, thank you. It's my pleasure to address the group. I'm representing the American College -- the American Association of Neurological Surgeons and the Congress of Neurological Surgeons.

I wanted to speak just very briefly about facet screws and just to point out the fact that we have information starting in 1944 on the clinical use of these type of devices and this has been well recorded in the literature. There's been a tremendous amount of information brought forward about these products, perhaps not in the most scientific method, but certainly in a practice-type method over the years and that the clinical results have shown safety and efficacy, cost efficiency.

In these difficult times, I think this is very important to be able to continue to utilize products that have been proven to be effective and efficient for our patients. And in speaking with my colleagues of the AANS and the Congress of Neurological Surgeons, we are in support of reclassification of the facet screws based on its initial publication in 1944 and subsequent clinical use over the past decades.

Thank you.

DR. SMITH: Thank you to our speakers.

Does anyone on the Panel have any questions?

(No response.)

DR. SMITH: If there are no current questions, I will move forward and now pronounce the Open Public Hearing to be officially closed. We will proceed with today's agenda.

I would like to introduce Dr. Constance Soves, who will be providing a classification and reclassification overview to the Panel. Constance Soves joined the FDA 9 years ago as a lead reviewer in what is now the Office of Orthopedic Devices, and currently serves as a regulatory advisor in the Office of Product Evaluation and Quality. She holds a bachelor of science in engineering degree from Princeton University, a master's degree in mechanical and biomedical engineering, as well as a doctorate in biomedical engineering from the University of Michigan.

DR. SOVES: Hello, my name is Constance Soves and I am a regulatory advisor within CDRH's Office of Product Evaluation and Quality. I will be providing you with a high-level overview of medical device classification and reclassification processes which form the basis for our discussions over the next 2 days.

The purpose of this panel meeting is twofold. The first part, which will be discussed later today, is regarding the reclassification of noninvasive bone growth stimulator devices. Specifically, the Panel will be asked to discuss the available scientific evidence regarding noninvasive bone growth stimulator devices, which are currently regulated as Class III devices. The Panel will also be asked to recommend whether they should remain in Class III or be reclassified to Class II.

The second part of the meeting, which will occur over the next 2 days, will be regarding the classification of devices that are currently unclassified. Specifically, for four preamendment unclassified device types, the Panel will be asked to provide input to the FDA on the appropriate classification (Class III, Class II, or Class I) for each device type.

Let's start by explaining the different classes of medical devices. Devices are

classified based on the controls necessary to mitigate the risks associated with a device type. Class I devices are only subject to general controls. Class II devices are subject to both general and special controls. And Class III devices are subject to general controls and premarket approval. These regulatory controls will be discussed in greater detail in the following slides.

Importantly, a device should be placed in the lowest class whose level of control provides a reasonable assurance of safety and effectiveness.

Now I will go into a bit more detail about each of the classes. Again, Class I devices are those devices for which general controls are sufficient to provide a reasonable assurance of the safety and effectiveness of the device. General controls are basic requirements that apply to all medical devices and are outlined in the Federal Food, Drug, and Cosmetic Act. Some examples include meeting establishment registration and device listing requirements, following good manufacturing practices, adhering to recordkeeping and reporting requirements, and ensuring that devices are not misbranded or adulterated. Most Class I devices do not require FDA premarket review prior to being marketed.

On the right-hand side of this slide you can see a few examples of Class I devices. These include hospital beds, ostomy bags, and certain manual surgical instruments.

There's also an alternative pathway to determine a medical device is Class I. Class I devices could also be devices that cannot be classified into Class III because they're not life-sustaining, life-supporting or of substantial importance in preventing impairment of human health, and they do not present a potential unreasonable risk of illness or injury, and these devices cannot be classified into Class II because insufficient information exists to establish special controls to provide a reasonable assurance of safety and effectiveness.

Class II devices are those devices which cannot be classified into Class I because general controls by themselves are insufficient to provide reasonable assurance of the

safety and effectiveness of the device, and for which there is sufficient information to establish special controls to provide such assurance.

There are many types of special controls, but some examples include performance testing, sterilization validation, and device-specific labeling requirements. These special controls, in combination with the general controls previously described, provide a reasonable assurance of safety and effectiveness for Class II devices.

Examples of Class II devices include nasogastric feeding tubes, semi-constrained metal-on-polymer knee replacements, and surgical sutures.

Typically, Class II devices require a premarket notification, generally referred to as a 510(k), prior to being marketed in the U.S. Within these 510(k) submissions, companies must also provide evidence demonstrating how the special controls for this specific device type are met.

Class III devices are those which cannot be classified into Class II because insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device, and the devices are life-sustaining or life-supporting, or are of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness of injury. Class III devices typically require premarket approval through a premarket approval application, or PMA, prior to being marketed.

Examples of Class III devices include pacemakers, vascular stents, and implanted urinary and fecal incontinence devices.

Here you can see a flowchart which walks through the general decision-making process for each of the classes that was just discussed. We start with determining whether general controls are sufficient. If so, the device can be appropriately regulated in Class I. If not, we ask whether there is sufficient information that allows us to be able to develop

special controls. If so, the device can be appropriately regulated in Class II. If not, then it would be Class III if the device is life-supporting or life-sustaining, or if it is of substantial importance in preventing impairment of human health, or if it presents a potential unreasonable risk of illness of injury. If the device is not life-supporting or life-sustaining, or of substantial importance in preventing impairment of human health, and does not present a potential unreasonable risk of illness or injury, then we end back up at a Class I designation.

Now we will shift our focus specifically to the discussion of reclassification of noninvasive bone growth stimulator devices.

What is the process for this reclassification? The decision to initiate this process is based on new information about the device, either on FDA's own initiative or upon the petition of an interested person. When going through this process, FDA considers intended uses which have been reviewed in the context of premarket review.

The first step in this process is to publish a proposed order announcing FDA's proposed classification and seeking public comment. This step has already been completed. The associated proposed order was published in the *Federal Register* on August 17th, 2020 and is being followed by a 60-day comment period.

The second step is to convene a panel meeting to discuss the proposed classification. This step is being completed today.

The final step will be to consider public comments received and all available information, including panel recommendations, prior to issuing a final order.

What we ask from the Panel today is to review and discuss available scientific evidence regarding the safety and effectiveness of noninvasive bone growth stimulators. The input and recommendations should include

- An identification of the risks to health presented by the device;

- A discussion of whether the device is life-supporting/life-sustaining, of substantial importance in preventing impairment of human health, or if it presents a potential unreasonable risk of illness or injury;
- A discussion of whether sufficient information exists to develop special controls;
- An identification of those special controls; and
- A discussion of whether general controls are sufficient by themselves.

After this panel meeting, FDA will consider all available evidence, including the input received today from this Panel along with any public comments.

FDA will then issue a final order which identifies the appropriate classification of the device. If these devices are determined to be Class I, they may continue to be marketed. Similarly, if FDA determines that these devices should be retained in Class III, devices which have already been approved through the PMA process can remain on the market. If FDA determines that the devices can be appropriately regulated as Class II devices, however, existing devices may remain on the market provided that they meet the designated special controls. Further details regarding the specific implementation strategy would be outlined within the final order.

Finally, we will discuss the classification process for the preamendments unclassified device types which will be discussed over the next 2 days. Before we walk through the process, here are a few quick definitions.

First, what is a preamendments device? A preamendments device is a device which was introduced into interstate commerce prior to May 28th, 1976 or the date of enactment of the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act.

An unclassified device is a preamendments device which was not classified by the original classification panels; therefore, no classification regulation currently exists for these

devices.

This brings us to the second purpose of this panel meeting, to formally classify these unclassified devices. Please note that while these devices are not classified, they are currently brought to market through the 510(k) process.

These preamendments unclassified devices will be classified once the FDA has taken the following steps:

First, FDA will solicit input and a recommendation from the device classification panel.

Second, FDA will publish the Panel's recommendation for comment, along with a proposed rule outlining FDA's proposed classification for the device.

Finally, after taking into account public comments, the FDA will publish a final rule classifying the device.

What we ask from the Panel today is to provide input on the classification of these unclassified device types and whether they should be classified into Class III, Class II, or Class I.

The input should include

- An identification of the risks to health presented by the device;
- A discussion of whether the device is life-supporting/life-sustaining, of substantial importance in preventing impairment of human health, or if it presents a potential unreasonable risk of illness of injury;
- A discussion of whether sufficient information exists to develop special controls;
- An identification of those special controls; and
- A discussion of whether general controls are sufficient by themselves.

Following this panel meeting, the FDA will consider all available evidence, which

includes the input received from this Panel and the public. The FDA will then publish a proposed rule in the *Federal Register* proposing classification of these device types and seeking public comment on the proposal.

Finally, FDA will issue a final rule identifying the appropriate class. If FDA determines that the devices can be appropriately regulated as Class I or Class II devices, the devices may continue to be marketed. If, however, FDA determines that they fall into a Class III designation, a separate call for PMAs will also be published. Existing devices may remain on the market until a specified date at which point a PMA should be submitted in order to continue marketing. If this PMA is not approved, devices would be considered misbranded and must be removed from distribution.

I hope that this has provided you with sufficient background to set the stage for the forthcoming discussions. Thank you for your time and attention.

DR. SMITH: I would like to thank Dr. Soves for her presentation.

Does anyone on the Panel have a brief clarifying question?

(No response.)

DR. SMITH: We will now hear a presentation of the FDA. I will now introduce the FDA review team.

Brittany Ferrell has obtained her bachelor of science degree in material science and engineering from Virginia Tech. She's a lead reviewer in the Extracolumnar Spinal Devices Team and has been with the FDA for 11 years.

Vikansha Dwivedi has been with FDA for approximately 4 years. Before joining the Agency, she obtained her bachelor of science in mechanical engineering from the University of Maryland. She is currently a reviewer in the Intracolumnar Spinal Devices Team.

Dr. Moazzam is a medical officer in the Extracolumnar Spinal Devices Team. She completed orthopedic surgery residency at Kansas University Medical Center in Kansas City,

Kansas, and fellowship at Johns Hopkins University in Baltimore, Maryland. Prior to joining the Agency 3 years ago, Dr. Moazzam was in clinical practice in Northern Virginia.

FDA, you have the floor.

DR. MOAZZAM: Good morning and welcome to the FDA panel meeting. My name is Dr. Caroline Moazzam and I am a medical officer in FDA's Office of Product Evaluation and Quality, Office of Health Technology 6: Office of Orthopedic Devices. I am a member of the FDA facet screw classification team, additionally comprised of my colleagues, Brittany Ferrell and Vikansha Dwivedi. Brittany and Vikansha are both lead reviewers in the Division of Spinal Devices.

Together, we will be presenting information regarding our efforts to classify devices under our jurisdiction which are not currently classified as Class I, II or III as defined by the Federal Food, Drug, and Cosmetic Act. These devices are called preamendments devices as they were first marketed in the U.S. prior to 1976.

Specifically, I will present information regarding facet screw spinal device systems under product code MRW, in an effort to classify these devices. I will provide a device description, indications for use, regulatory history, and clinical background of these devices. I will then present our review of the safety and effectiveness of these devices based on our review of published literature as well as additional information available to the FDA, specifically the Manufacturer and User Facility Device Experience, or MAUDE, and Recalls databases. I will present our review of risks posed by these devices and proposed mitigations for these risks in our ongoing efforts to protect and promote public health.

After I present the totality of our review, my colleague, Brittany Ferrell, will propose classification regulation for these devices. Finally, she will ask you, our convened Panel, to determine whether you agree with:

1. Our assessment of risk;

2. The adequacy of our proposed mitigations to achieve a reasonable assurance of safety and effectiveness; and ultimately
3. Our classification recommendation.

Let us begin. Here is the outline for today's presentation. These are the items that we will be discussing.

Device description. Facet screw spinal device systems are intended to stabilize the spine to promote fusion through immobilization of the facet joints in the cervical, thoracic, and lumbosacral spine.

These devices and associated surgical techniques have been described since the 1950s. They consist of partially or fully threaded bone fixation screws used without longitudinal members such as spinal rods and spinal plates. They are manufactured from titanium alloy per ASTM F136 or stainless steel per ASTM F138.

These devices are reportedly used unilaterally or bilaterally, with or without bone graft material, and have been cleared with other accessories such as washers and cross-connectors. When used unilaterally, these devices have been described as used contralaterally to posterior spinal instrumentation.

These diagrams depict two examples of posterior facet screw fixation in spinal models. Figure A depicts the transfacet technique described in 1959 by Boucher. This technique uses two screws for each level, one per side, traversing the facet vertically from medial to lateral.

Figure B depicts the translaminar technique described in 1984 by Magerl. In this technique, the screw enters through the base of the spinous process on one side, fixes the contralateral facet joint after traversing the lamina, and ends at the base of the transverse process.

Though the screws have different trajectories, both techniques aim to stabilize the

facet joint to promote fusion. These diagrams are representative and are reproduced from the citation provided.

This is an additional posterior and lateral diagrammatic depiction of implantation utilizing the transfacet technique discussed in the previous slide. These images are representative and are provided by industry, specifically Globus Medical.

These devices have been cleared as an adjunct to fusion for the following indications for use:

- Degenerative disc disease as defined by back pain of discogenic origin with degeneration of the disc confirmed by history and radiographic studies;
- Degeneration of the facets with instability;
- Trauma, including spinal fractures and/or dislocations;
- Pseudarthrosis or failed previous fusion which are symptomatic or which may cause secondary instability or deformity; and
- Spondylolisthesis and spondylolysis.

Regulatory history. Facet screw spinal device systems were manufactured by Zimmer Manufacturing Company prior to May of 1976 under the Townley Bone Graft Screw and Townley Headless Compression Screw trade names.

The first product code MRW device cleared under the 510(k) program, the Sofamor Danek transfacet pedicle screw fixation system was found substantially equivalent to the Zimmer preamendments predicate device on February 28th, 1997, under K953076. To date, the FDA has cleared a total of 55 devices under the MRW product code.

Clinical background. Facet screws are one type of implantable spinal device currently available for operative treatment of specific spinal conditions where stabilization of spinal segments as an adjunct to fusion or permanent immobilization is sought. Facet screws provide a biomechanically equivalent method of spinal fixation which potentially

avoids the need for implantation of longitudinal spinal rods.

A systematic literature review was conducted in an effort to gather any published information regarding the safety and effectiveness of facet screw spinal device systems under product code MRW. The searches were limited to publications in English.

The literature review assessed the effectiveness of bilateral and unilateral facet screw use in terms of fusion rates and improvement in pain and disability scores including Visual Analogue Scale, Neck Disability Index, Oswestry Disability Index, and safety in terms of adverse events.

Literature review effectiveness assessment. For the publications which referenced use of hybrid instrumentation, treatment outcomes could not be directly attributed to the use of facet screw instrumentation alone. However, the use of hybrid instrumentation achieved comparable fusion rates compared to the use of traditional bilateral pedicle screw systems, which are Class II devices.

The bilateral and unilateral use of facet screw spinal device systems were reported to have similar safety profiles with respect to fusion rates and improvement in VAS and ODI scores when compared to traditional bilateral pedicle screws.

Publications reported fusion rates for the bilateral, unilateral, and hybrid facet screw use which ranged from 93.5 to 100%. Improvement in VAS and ODI scores were also reported in the reference publications.

Additionally, several publications reported no significant differences in fusion rates or pain and disability scores when compared to traditional bilateral pedicle screw use.

Based on our safety assessment of our literature review, adverse events reported for bilateral and unilateral facet screw use include:

- Screw fracture and breakage
- Screw loosening

- Screw pull-out
- Screw misplacement
- Infection
- Reoperation
- Non-fusion
- Foraminal encroachment
- Facet injury
- Lamina invasion or penetration

In summation, what we concluded from our literature review is as follows: The reported adverse events are similar to those observed with the use of other Class II spinal instrumentation systems and do not raise any additional concerns.

The facet screw spinal device systems were reported to have similar safety and effectiveness profiles as pedicle screw systems when used as adjuncts to fusion for the permanent immobilization of spinal segments.

Based on the review of the published literature, the clinical evidence supports a reasonable assurance of safety and effectiveness for facet screw use as a method of providing immobilization and stabilization of the spine as an aid for fusion.

The Manufacturer and User Facility Device Experience, or MAUDE, database houses medical device adverse event reports submitted to the FDA by mandatory reporters such as manufacturers, importers, and device user facilities, as well as voluntary reporters such as healthcare professionals, patients, and consumers.

The MAUDE database contains mandatory reports filed by manufacturers and importers from August 1996 to the present, all mandatory user facility reports from 1991 to the present, and voluntary reports filed after June of 1993. Each year, the FDA received several hundred thousand medical device reports of suspected device-associated deaths,

serious injuries, and malfunctions. Medical device reporting or MDR, is one of the postmarket surveillance tools the FDA uses to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products.

The major utility of MDRs in general is that they can provide a qualitative snapshot of a device's adverse event profile during real-world use. Review and analysis of MDRs may provide information on the types of events being seen along with their severity, clinical consequences, and treatments needed to address these issues. Changing trends in these parameters over time may also be noted.

In addition, MDRs submitted by manufacturers also include their evaluation of the event, which at times may include assessment and testing of a returned product.

Although MDRs are a valuable source of information, this passive surveillance system has limitations. It is important to understand the limitations of this system in order to put the numbers and reports into perspective.

Among the limitations includes the submission of incomplete, inaccurate, untimely, unverified, or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to underreporting of events, inaccuracies in reports, lack of verification that the device caused the reported event, and lack of information about the frequency of device use. Because of this, MDRs comprise only one of the FDA's several important postmarket surveillance data sources.

FDA reviewed our MAUDE and Recalls databases for additional information regarding risk identification in our safety analysis of facet screw spinal device systems. Searching the MAUDE database yielded 96 adverse event reports for product code MRW from February 28th, 1997 through January 27th, 2020. February 28th, 1997 was the date of the first FDA clearance.

The majority of the reported adverse events, specifically 49 out of 96 or 51%, were

related to instrument- or implantation-specific malfunctions. Twenty-five out of 96 or 26% were fracture, loosening, and migration, which comprised device- or implant-specific adverse events. These are considered anticipated adverse events for spinal implants. The remaining reports, 22 out of 96 or 23%, did not specifically describe events related to device failure. No deaths or serious neurological injuries were reported.

Our second exclusively available data source is our Medical Device Recalls database, which contains medical device recalls dating back to November of 2002. From November 2002 through January of 2020, a total of three recalls have been reported for devices with the product code MRW.

The first recall involved two implant driver assembly tips breaking intraoperatively. The second and third recalls were due to pull pins potentially disengaging from facet screws during attempted compression, which required compression with the device driver rather than the compression tool. The identified recalls are related to instrument issues and do not suggest safety concerns related to facet screw spinal device systems as a product class.

In summation, and based on the totality of the review of the literature, as well as the MAUDE and Recalls databases, FDA identifies no new general safety concerns related to facet screw spinal device systems as a product class. These sources have identified common risks associated with these devices for which we will propose mitigations in the next slide.

Please now turn your attention to my colleague, Brittany Ferrell, who will propose risk mitigation and classification regulation for these devices.

MS. FERRELL: Thank you, Dr. Moazzam.

Hello, my name is Brittany Ferrell, a lead reviewer in the Division of Spinal Devices. To determine the appropriate classification for facet screw spinal devices, we have identified risks associated with these devices and possible mitigations for these risks. We'll

be asking the Panel for input on the list of risks and mitigations.

To identify the risks of these devices, we used FDA's MAUDE database to identify MDRs, the information available to FDA regarding cleared devices, and the previously discussed literature review. We identified the following six risk categories for facet screw spinal devices.

Loosening or migration due to device failure or failure at the bone/implant interface. The components may deform, fracture, wear, loosen, or disassemble, resulting in a mechanical or functional failure which may result in back or leg pain, neurologic deficit or injury, or loss of correction. Additionally, components may loosen, migrate, or disengage from the bone, which may result in back or leg pain, neurologic deficit or injury, or loss of correction.

Tissue injury. Intraoperative and postoperative risks of tissue injury include:

- Bone fracture
- Injury to blood vessels or viscera
- Neurologic injury
- Dural tear
- Cerebrospinal fluid leak
- Skin penetration or irritation

Postoperative wound problems include infection and hematoma or seroma.

Adverse tissue reactions. Device materials may elicit adverse tissue reactions such as foreign body response, metal allergy, and metal toxicity.

Use error or improper device use. Risks of device malposition may include difficulty or inability to implant the device components or incorrect placement of the device.

Pseudarthrosis due to device failure or failure at the bone/implant interface. The risk of nonunion pseudarthrosis signifies failure of bony fusion and potential instability or

765 pain.

766 Adverse clinical sequelae. Adverse clinical sequelae may include the risk of new or
767 unresolved pain, new or worsened neurological deficit or injury, or loss of correction.

768 The table on this slide outlines the identified risks to health for this device type, and
769 the recommended controls to mitigate the identified risks. FDA believes that special
770 controls, in addition to general controls, can be established to mitigate the risks to health
771 identified and provide a reasonable assurance of safety and effectiveness of facet screw
772 spinal device systems. We propose that these mitigations can be implemented as special
773 controls as part of the device regulation process.

774 We propose to identify the device as follows: Facet screws are bone screws
775 consisting of solid or cannulated designs with fully or partially threaded screw shafts used
776 without longitudinal members (for example, spinal rods or spinal plates) indicated for use
777 for stabilization of the spine to promote fusion by immobilization of the facet joints. Facet
778 screws may be used with additional components that are part of the device system, such as
779 facet washers and accessory instrumentation.

780 Based on the information presented, FDA is proposing Class II with special controls
781 for facet screw spinal device systems.

782 Special controls are intended to mitigate the risks specific to these devices, and in
783 combination with general controls are necessary to provide a reasonable assurance of
784 safety and effectiveness for this device type.

785 The proposed special controls of this device are as follows:

786 • Design characteristics of the device, including engineering schematics, must
787 ensure that the geometry and material composition are consistent with the
788 intended use.

789 • Nonclinical performance testing must demonstrate the mechanical function

and durability of the implant.

- Device must be demonstrated to be biocompatible.
- Validation testing must demonstrate the cleanliness and sterility of, or the ability to clean and sterilize, the device components and device-specific instruments.
- Labeling must bear all information required for the safe and effective use of the device, specifically including the following:
  - Clear description of the technological features of the device, including identification of device materials and the principles of device operation;
  - Intended use and indications for use including levels of fixation;
  - Identification of magnetic resonance (MR) compatibility status;
  - Cleaning and sterilization instructions for devices and instruments that are provided non-sterile to the end user; and
  - Detailed instructions on each surgical step, including device removal.

And that concludes our presentation. Thank you.

DR. SMITH: I would like to thank the FDA experts for their very thorough presentation.

I want to open the floor to the experts around the table to begin deliberating on this topic, considering everything you have read in your panel packs and heard in today's Open Public Hearing and presentations.

Although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair. Additionally, we request that all persons who are asked to speak identify themselves each time. This helps the transcriptionist identity the speakers.

Let us begin. Do any Panel members have a question or a comment for the FDA? Panel, please turn on your video monitors and unmute your computer when you speak. You may raise your hand and I will call on you.

All right. Yes, Dr. Finnegan.

DR. FINNEGAN: So I have two questions. One is, you may or may not have an answer to, the standard cannulated screws that are used in trauma, other than the spine, what class are they? Because they would've been since 19 -- since you started classifying.

MS. FERRELL: Hi, this is Brittany Ferrell. Our trauma screws are Class II, as well.

DR. FINNEGAN: Okay. And then my second question is given when these were introduced, have there been any good mechanical studies as far as two things, one is pull load and the second is do they need extra stabilization such as bracing or other forms of stabilization or can they function by themselves?

MS. FERRELL: And I may have a medical officer answer that, Caroline.

DR. MOAZZAM: Hi, Caroline Moazzam. I am not aware of any studies that specifically address your question.

DR. SMITH: A number of hands went up earlier. Please raise your hand again if you have a question.

Yes, Dr. Yang.

DR. YANG: I have two questions with regard to risk. When you presented the data on the risk, you included the MAUDE data with 96 adverse events in some very broad categories. What I would like to know is if you know any specifics regarding the number or percentage of either CSF leaks or neurological injury, actual nerve root injury or CSF leaks leading to intraspinal nerve root injury.

DR. MOAZZAM: Hi, it's Caroline Moazzam again. Thank you for your question. Unfortunately, the data that we receive from these databases is sparse. We are limited to

what has been submitted to us and we do not have the delineation that you're requesting.

DR. YANG: Thank you.

DR. SMITH: Yes. And may I ask you, please introduce yourself.

DR. EBRAMDAZEH: This is Eddie Ebramzadeh from UCLA. So a specification, a proposed specification includes biocompatibility which, of course, we know the materials that are proposed and used commonly for screws are biocompatible, titanium alloy or stainless steel.

However, what's not discussed or specified in these lists that I saw is the surface texture of the screws. The texture will affect the adhesion and on-growth of the bone over time and especially since this is a very delicate and small structure, the facet, if removal or turning back is necessary, then it could affect the strength of adhesion and therefore produce a risk if it's too rough.

So I think that's something that needs to be discussed and considered in the manufacture of these. It's not just material and geometry, but also the surface finish of the screws. We know this from going back to dental implants and fracture fixation devices, that it's an important factor. In some cases in long bones, it may not matter so much if the adhesion is large, but in this case, I think -- I realize that these are rarely removed, but if the occasion arises.

DR. SMITH: Are there additional questions or comments?

MS. FERRELL: Hi, this is Brittany Ferrell. I just wanted to note that surface texturing is noted. We have paid more particular attention to spinal screws that have had unique texturing in the past.

DR. SMITH: Yes, Dr. Alander.

DR. ALANDER: I was wondering, in the literature review, if you were able to parcel out those studies that looked at this as an adjunct to fusion, i.e., using an interbody device,

a posterior interbody device for a fusion and this is adjunct to that versus just using this as standalone. So my concern here is what are we talking about, you know, preparation of the facet surfaces to allow for fusion, are we using this as an adjunct?

DR. MOAZZAM: Caroline Moazzam again. We did look at studies that used this independently of interbody devices. We did, however, have difficulty in limiting the benefits to the construct, specifically the facet screws alone, so we did try to indicate that in our literature review. They did indicate that they were similarly performing as traditional pedicle screws. So when they were used adjunctively, they were used similarly as a pedicle screw would've been used adjunctively.

DR. SMITH: Are there additional questions?

DR. GILBERT: Dr. Smith, I'm not sure how to raise my hand, this is Jeremy Gilbert calling, so I'd like to ask one or two questions, if I may.

DR. SMITH: Yes, sir.

DR. GILBERT: So two questions, really. In the identification of the risks with this facet screw there was mention of toxicity and allergy associated with the devices and then also the nature of the degradation processes that go on with screws included things like wear and fracture and so on. And really, I think one of the mechanisms that needs to be explicitly called out, if allergy and toxicity are concerned, is corrosion because, really, you need to have electrochemical reactions releasing metal ions for those to induce an allergic response. It won't solely be by a wear mechanism. We know, in the literature, if wear occurs of a metal surface there are associated corrosion reactions that take place. So I think that may need to be somehow included in that discussion.

And then secondly, sort of associated with that, when testing to mitigate the risks, one of them was biocompatibility, Dr. Ebramzadeh talked about that a little bit and it's a very broad term, it's very nondescript and I don't know if there is a more specific set of

biocompatibility tests that are envisioned here or parameters about which to define such tests or if it's just go look at the ISO 10993 standard and perform all of the tests there. So I'm just curious about what that biocompatibility statement means.

MS. FERRELL: Hi, this is Brittany Ferrell. All of our 510(k) devices are reviewed for biocompatibility, we look at the material to see if there's any other information that's needed that we can determine that it's equivalent to another predicate device. We do have additional tests -- that we need to review for these devices.

DR. SMITH: Yes, Mr. O'Brien.

MR. O'BRIEN: Yes, thank you. My question for Brittany and Dr. Moazzam and Vikansha is regarding the risk identification of improper use or improper positioning of the device, of the adverse events concerning MAUDE, from a patient perspective, of the neurological deficits, how much were attributed to that? And my question, I guess, with that is with special controls, it's identified as labeling. Is labeling by itself without device training and navigation systems adequate for our patients?

DR. MOAZZAM: Hi there, it's Caroline Moazzam again. I can take the part about the databases that we have. Unfortunately, our databases don't provide the granularity that allow us to have any more specifics regarding the patient-specific outcomes in a reported adverse event. So that's all the way of saying we don't know more than what we presented to you.

MR. O'BRIEN: Well, I guess if I may, just a follow-up. Under special controls, beyond the labeling is there another requirement regarding -- potential requirements regarding education, training or navigation systems, etc., that enhance the use of that device?

DR. MOAZZAM: So I will defer specific questions about special controls to my colleague, Brittany Ferrell.

MS. FERRELL: So hi, this is Brittany Ferrell. So training is recommended, the

technique is unique. However, labeling is the best of where it shows how to actually use the device. And again, these screws have been used for almost 60 years, so a cleaner technique is out there and they've been used in a similar manner that's out there, so we believe labeling -- for example, this is a -- is sufficient to demonstrate how these devices can be used. And additionally, we have a number of devices that have been cleared already, as we stated in our presentation, I believe 55 have been cleared.

DR. SMITH: Are there any additional questions or comments?

DR. PRICE: Yes, this is Amy Price. And I believe it was Dr. O'Brien (sic) that mentioned patient-specific outcomes are apparently not available. I'm wondering if that could possibly be made a part of the mitigation strategies. And in the same kind of direction, the functional status, is the functional status determined, the functional mechanical status, is that determined on people, like with people or is that just mechanically determined? And what's the evidence for that with people? Like, do we have randomized controlled trials, do we have observational studies? Like, what's available?

MS. FERRELL: This is Brittany Ferrell. Can I ask as a quick follow-up? Can you expand on when you referred to patient-specific outcomes, are you asking for us to look into that, like ask for the databases to provide this information or can you just expand on that question, please?

DR. PRICE: Yes, I'm asking could patient-specific outcomes be included in the database and reported on since the patients are actually the ones that are going to be living with the outcomes of the device, whether -- like whether good or bad. And it seems reasonable to include the outcomes that are important to them. They could be developed by patients along with researchers and clinicians, and then there would be a nice list of things that get noted and that made a difference. So then it would give us a better idea of where a device fit in terms of classification.

DR. MOAZZAM: Hi, this is Caroline Moazzam again. Thank you so much for your comment. These devices have been on the market for quite a few decades. We've gone ahead and reviewed all of the literature available for a pretty long period of time. In regards to our specific databases, in order to protect patient privacy and because these are voluntary reports, there aren't specific patient identifiers provided.

So to try to answer your question as succinctly as possible, these are devices that have been on the market for quite a period of time and because they have been on the market since before our classification, they have not been classified previously. So their lack of classification is more just how long they've been on the market, not for any other reason.

DR. PRICE: I think are we saying that there's no specific patient-specific outcomes in the literature that you looked at for these devices, but you want to classify them just on terms of age?

DR. MOAZZAM: There are no specific studies addressing patient-reported outcomes that we were able to obtain that we did not already include in our presentation.

DR. PRICE: Okay, thank you.

DR. SMITH: Are there any additional questions or comments?

(No response.)

DR. SMITH: If there are no additional questions or comments, at this time let us focus our discussion on the FDA questions. Copies of the questions can be found in your electronic documents and on the FDA website. I want to remind the Panel that this is a deliberation period among the Panel members only. Our task at hand is to answer the FDA questions based on the data in the panel packs, the presentations, and the expertise around the table. I will now read Question Number 1.

FDA has identified the following risks to health for facet screw spinal device systems:

- Loosening or migration
- Tissue injury
- Adverse tissue reactions
- Use error or improper device use
- Pseudarthrosis
- Adverse clinical sequelae

Please comment on whether you agree with inclusion of all of the risks in the overall risk assessment of the facet screw spinal system devices under product code "MRW." In addition, please comment on whether you believe that any additional risks should be included in the overall risk assessment of these facet screw device spinal systems.

Yes, Dr. Alander.

DR. ALANDER: Dirk Alander. I'd like to comment, I think this is a pretty good list. I would add, and I would want to stress, that under pseudarthrosis, that it's very important that the principles of fusion don't get lost in using this device. I can just foresee, and I've seen in other instances with minimally invasive or usually applied techniques, that they get used but they -- that people aren't instructed, don't know or don't use the device appropriately in considering fusion techniques. And I guess I would like to highlight that in some way, shape or form that fusion techniques still are the basis for -- or principles, I should say, fusion principles are really what we need, what we're trying to do is get a fusion and these are only adjunct.

DR. FINNEGAN: I agree, I think they are appropriate and this is probably not the right place to put it, but I think that the problem is patient-specific outcomes is very new and so it wouldn't have been before and I don't know that it's necessarily a risk, but if you could somehow put outcomes somewhere in the -- not in the discussion, but in your assessments, that would be, I think, very appropriate. Otherwise, I think these are good.

DR. SMITH: Thank you, Dr. Finnegan.

Dr. Yang, you had your hand raised?

DR. YANG: Yeah. In the same vein, I want to advocate for something, which is under adverse clinical sequelae, the new and unresolved pain and loss of correction is lumped right in there with new or worsened neurological deficit and injury. Given our patient-centered and patient outcomes, patient-reported outcomes emphasis, it seems to me like a new neurological deficit, a loss of a particular function, nerve root, etc., is actually significantly different than worsened pain or anything like that. So in that same vein, I'd like to advocate for the idea that the neurological injury category should probably be something separate and just as important.

DR. SMITH: Thank you.

Dr. Ebramzadeh, you had your hand up?

DR. EBRAMDAZEH: Yes. I'm not sure if we discussed the possibility of device fracture or bone fracture. Was that one of the risks that was never observed or reported or -- I don't see it in the list of risks and I would imagine that it's a concern, but could the Panel comment on that?

DR. SMITH: I would comment, in the loosening/migration category, a subset of that is a failure of the device, specifically component deformation, fracture, wear, or loosening or disassembly of the instrumentation construct.

DR. EBRAMDAZEH: I would think it should specifically be noted, but I see device failure, so that encompasses that, but maybe it should be specifically noted.

DR. SMITH: Dr. Elder.

DR. ELDER: Hi, Benjamin Elder. I would recommend specifically noting inadequate biomechanical fixation to allow for fusion as a specific risk. That could certainly be controlled for with biomechanical data. Then I agree with Dr. Alander's comment on

specifically looking and allowing fusion and maybe adding a specific risk of obstructing fusion surfaces across the facet joint.

DR. SMITH: Are there any additional comments for this question?

(No response.)

DR. SMITH: We will move on to Question 2. Please discuss whether the identified special controls described in the FDA questions found in your panel materials for facet screw spinal device systems appropriately mitigate the identified risks to health and whether additional or different special controls are recommended.

Dr. Finnegan.

DR. FINNEGAN: Maureen Finnegan. I finally learned to say my name. I would like to reinforce under the design characteristics and the nonclinical performance that it does not appear that there's been any pull-out strength or any suggestion that there might need to be additional stability, such as the interbody fusion, in order for these to fuse. So I think some of that needs to be included in those first two points.

DR. SMITH: Dr. Alander.

DR. ALANDER: Yes, just to clarify, I think that just compression alone isn't going to guarantee a fusion and that's kind of what it comes down to from a spine fusion principle standpoint.

DR. SMITH: Are there any additional comments for this question?

Yes, Dr. Gilbert.

DR. GILBERT: Let me turn my microphone on. Jeremy Gilbert. I'd like to come back to this question about biocompatibility just for a second. Biocompatibility testing can take many forms, but I've yet to see a good biocompatibility test that can assess adverse tissue reactions, for example. I've not seen a biocompatibility test that can assess pseudarthrosis, either. You know, these are challenging, difficult things to do and I'm just curious about can

we expound on what are we talking about, an animal model that can mimic the kinds of failure modes that then can be assessed for an appropriate response? I'm not clear on what it means to say biocompatibility to test adverse tissue reaction or pseudarthrosis.

(Pause.)

DR. ALANDER: Can't hear you.

DR. SMITH: Dr. Alander.

DR. ALANDER: Dirk Alander. Jeremy, I guess I understand your question. I guess that in this case the implants are already using metals and alloys that we've been using for years and years in pedicle screws and rods, you know, chrome-cobalt, titanium, stainless steel. So I don't think that that's a big issue in this sense because they've already been used, and forever. But I understand where you're coming from.

DR. GILBERT: Jeremy Gilbert. Thanks, Dirk. I agree, I mean, these metals have been used for decades in wide-ranging applications throughout the body and I think we understand a lot about what goes on with them. And I think my question is more -- maybe more general beyond the facet screw, just in terms of how FDA assesses in a 510(k) application when a device is being proposed for marketing. And, you know, we use a word like biocompatibility and it doesn't mean the same thing to everybody and it's sort of unclear and in the specific case of facet joints, I think we do know what happens in terms of the metal's interaction with the body, for the most part. And so just to say, as a special control, we're going to do biocompatibility, to me, doesn't really answer it for this case or for any other case.

DR. ALANDER: Agreed.

DR. SMITH: Are there any additional comments for Question 2?

DR. PEAT: This is Captain Peat, can I say something really quickly? I know there's been a lot of discussions regarding biocompatibility and I can tell you that, over the course

of the years, we have really drilled into each of our applications, whether they're going to be 510(k) or PMAs or de novos or what have you, and looking at biocompatibility. Now there are a number of standards as well as guidance documents that speak to the devil of the details for biocompatibility and do note that if they're novel devices, we really do look for more information regarding biocompatibility. So I don't think it's just a broad sense of the term. We are looking at those specific areas within biocompatibility for each of our products that are going to be cleared or approved.

DR. SMITH: Dr. Bonnell (sic), did you have a question?

MS. BONNELL: Yes. Hello, Stacey Bonnell, non-voting Industry Rep. So Captain Peat detailed some of the same types of standards, that there are recognized standards for a majority of these mitigaters, including biocompatibility as well as nonclinical performance testing.

I'm also aligned with the prior discussion in terms of identified risks and the recommendations to those risks. Comparing this list of risks from the panel pack, the recommended mitigation measures, I do think that the special controls as listed here are appropriate and consistent with other fusion spinal systems that are already promulgated as moderate risk Class II devices.

DR. SMITH: Are there additional comments?

DR. PRICE: This is Amy Price. I'm concerned that the biocompatibility is built on predicates. So if there is like, for instance -- I know this is not the same situation, but with hips, metal-on-metal, for example, and the -- you know, the tissue issues there, that device was approved, I believe, as biocompatible and I am wondering, in this list, what could we do to mediate that happening again? You know, perhaps even the patient-specific outcomes might help because you would get the results over time, but I'm a little concerned that we're going to make a decision on predicates and biocompatibility without any direct

evidence.

DR. SMITH: Yes, Stacey Bonnell.

MS. BONNELL: Stacey Bonnell, Industry Rep. I just want to point out that substantial equivalence to biocompatibility wouldn't be a precursor within the premarket notification, that you'd be establishing substantial equivalence to the intended use and the technological parameters of the predicate device, not necessarily the biocompatibility. So that's where that standards discussion comes in, that there are notable recognized standards conformance documents that are specific to each functional area, nonclinical performance testing being one, and then biocompatibility as well as sterilizing and others, but they would need to demonstrate conformity to -- as opposed to conforming to a predicate device.

Does that help, Dr. Price?

DR. PRICE: Yes, somewhat. It's just we've got the nonclinical testing, so non-human, basically not in a clinical setting, and we have the -- like the choice is based on predicates and we don't seem to have evidence over time except that these devices have been in use for a long time and I think the challenge is that health literacy is only now coming to the surface along with things like patient-reported outcomes.

And so even if those devices were causing problems, they would not necessarily have been reported and so this is actually the concern that I have because a device that's leaking out metal or whatever and causing irritation or adverse events in that particular area, it might be perfectly fine at the time that it's implanted and then over time that might not be so fun, but it's all being improved already. So I'm wondering what we could do to mitigate that to make it more safe for our patients who are having these devices installed over time.

DR. PEAT: Yeah, this is Captain Peat, may I take a little bit of liberty? Amy, I do believe that you provided some really good comments regarding the thought process as to

making sure that we're doing the appropriate studies before we clear or approve our products as we're trying to bring these products into Class II with special controls. So I just want to make sure that I clear up some thought processes.

Whenever we are approving our 510(k)s, it's not necessarily we will look at just all of our studies related to the predicate devices. There may be nuances with this particular device we are reviewing and we are going to ask those key questions. You know, as time progresses when we're looking at biocompatibility, our studies or rigorous studies have vastly increased from, say, 5 years ago or 10 years ago and we're asking those specific questions such as leaching and looking at adverse tissue reaction.

So I can assure you that when it comes to risk of the particular material, even though this may come through as a 510(k) device, we are going to ask for those specific studies of that particular subject device. So I just wanted to assure you that it's not just a matter of looking at it side by side with the subject device and the predicate devices. Hence the reason why within our package you see that we put forward that there may be studies that are going to be asked so that we can ensure to mitigate any risk that comes about. Does that answer your question in a little bit more detail?

DR. PRICE: That helps, thanks very much.

DR. PEAT: You're welcome.

DR. ALANDER: Dirk Alander. Amy, if I could address some of your concerns here. Certainly, patient-reported outcomes are the big thing right now and the nice thing that has occurred is that there is a joint -- the registries that are occurring in the orthopedic world and so we have -- the American Academy of Orthopaedic Surgeons has a registry that is based on total joints, it's now included spine along with neurosurgery and that is going to give us a lot of the information, I think, that you want and we actually all want. But that's just up and starting and so we don't have access to all of the patient-reported outcomes

that we'd like, but the process is there and it's starting to work.

DR. PRICE: Thank you, thank you. Yeah, I appreciate that it may be in its infancy, but just to move it along. Thank you.

DR. SMITH: Dr. Gilbert, did you have a question? Or comment?

DR. GILBERT: No, I think the conversation has adequately addressed what I was going to ask.

DR. SMITH: Are there any other comments or questions with respect to Question 2?

(No response.)

DR. SMITH: Before we move on to Question 3, I'd like to summarize Questions 1 and 2.

Captain Peat, with regard to Question 1, the Panel generally believes that there is a long clinical history of these devices. The Panel did have some concern specifically with focusing on the roles of this sphere as adjunct devices and highlighted the need for a fusion technique and principles. There also was concerned raised regarding the need for patient-reported outcomes and that those should be included in assessing risks. There also was concern by some Panel members that neurologic deficit should perhaps be listed as a separate risk category. And there was also concern regarding if implant failure or fracture or bone fracture should be enumerated as a separate category. Also, there were concerns raised for Question 1 with respect to biocompatibility should be listed as a separate risk factor or complication.

Captain Peat, is this adequate?

DR. PEAT: Thank you, Dr. Smith, this is Captain Peat. I think that the responses provided by the panelists is adequate and we'll take all of the information that you've provided under consideration.

DR. SMITH: Thank you.

Captain Peat, with respect to Question 2, the Panel had some concerns of overlap of some degree with Question 1, specifically with respect to biocompatibility. There was a concern raised by some of us on the Panel regarding biocompatibility being aliased onto historical endpoints that were approved premarket prior. There also again was a note made with respect to Question 2 and patient-reported outcomes.

Captain Peat, is this adequate?

DR. PEAT: This is Captain Peat. Yes, this is adequate, what you've provided and we'll take it again under consideration. I think just the merger of Questions 1 and 2 really just highlights an additional risk that we should really parse out even though it was discussed within the Executive Summary, so thank you.

DR. SMITH: So at this point we will address Question 3. Please discuss whether you agree with the FDA's proposed classification of Class II with special controls for facet screw spinal devices. If you do not agree with the FDA's proposed classification, please provide your rationale for recommending a different classification.

Yes, Dr. Finnegan.

DR. FINNEGAN: Maureen Finnegan. I do agree with the classification and I also agree with moving neurological injury, in particular, to a separate category.

DR. SMITH: Yes, Dr. Yang.

DR. YANG: I just want to say that I also agree with the classification of these devices as Class II based on all the information provided.

DR. SMITH: Yes, Dr. Alander.

DR. ALANDER: I agree. I agree with Class II classification.

DR. SMITH: Dr. Gilbert.

DR. GILBERT: I do, as well.

DR. SMITH: Mr. O'Brien.

MR. O'BRIEN: I agree, as we did with pedicle screws, to define this as Class II.

DR. SMITH: I saw several hands going up at once that I'll call on sequentially.

Dr. Ballman.

DR. BALLMAN: Yeah, I just want to say, based on the definition provided and the information that was provided, I agree with Class II.

DR. SMITH: Dr. Ebramdazeh.

DR. EBRAMDAZEH: Based on the information provided, Class II specification is appropriate in my opinion.

DR. SMITH: Yes, Dr. Graf.

DR. GRAF: I also do agree with the FDA's proposed classification into Class II.

DR. SMITH: Yes, Dr. Elder.

DR. ELDER: I agree with Class II classification, as well.

DR. PFEFFER: Are you able to hear me? Glenn Pfeffer.

DR. SMITH: Yes, sir.

DR. PFEFFER: I just can't get my video on, but I agree with Class II. There you go, thank you for that. I agree with Class II.

DR. SMITH: Are there any additional comments?

(No response.)

DR. SMITH: Captain Peat, with regard to Question 3, the Panel unanimously agreed with classification as Class II. Captain Peat, is this sufficient?

DR. PEAT: This is absolutely sufficient, thank you very much.

DR. SMITH: Thank you. It's now approaching 9:50 a.m. We will take a quick 10-minute break. When we come back we will begin Session 2 concerning the noninvasive bone growth stimulator devices.

(Off the record at 9:43 a.m.)

(On the record at 9:53 a.m.)

DR. SMITH: We will now begin Session 2. The FDA will present on noninvasive bone growth stimulator devices. I will now introduce the FDA team. I will start with Shumaya Ali. Ms. Ali is an assistant director within the Restorative, Repair and Trauma Devices, the Office of Orthopedic Devices. She oversees the Stereotaxic. Bone Growth Stimulators. and Fracture Fixations Devices Team. Ms. Ali has been with the Agency for 10 years. She holds a bachelor of science in biology from the University of Maryland at College Park and a master of science in public health, health communication and marketing from the George Washington University Milken Institute School of Public Health.

Philip Belmont. Dr. Philip Belmont attained his B.S. from the United States Military Academy and his M.D. from Duke University School of Medicine. He completed his orthopedic surgery residency at Walter Reed Army Medical Center in Washington, D.C., and fellowship at the Anderson Orthopedic Clinic in Alexandria, Virginia. Dr. Belmont was a physician and orthopedic surgeon for 21 years in the Army, he has been a medical officer for the Knee Arthroplasty Team with the FDA for over 3 years.

Jesse Muir received his bachelor of science in biomedical engineering from Boston University and his doctorate in biomedical engineering from Stony Brook University. He is currently a lead reviewer in the Stereotaxic. Bone Growth Stimulator. and Fracture Fixation Devices Team. Dr. Muir has been a reviewer in the Office of Orthopedic Devices for 6 years and has over 15 years of experience in orthopedic research and regulation.

MS. ALI: Good morning and welcome to the FDA panel meeting. My name is Shumaya Ali, I'm an assistant director within the Division of Restorative, Repair and Trauma Devices, Office of Health Technology 6: Office of Orthopedic Devices. I will be joined by my colleagues, Dr. Philip Belmont, medical officer, and Dr. Jesse Muir, lead reviewer. In the remainder of today's panel we'll be focusing on a discussion and making recommendations

for the reclassification of noninvasive bone growth stimulators.

We have three presenters today, including myself. The topics that we'll be covering are outlined in this slide. I will be covering the purpose, device description, intended use and indications for use. I will also provide a high-level overview of FDA's rationale for the proposed reclassification.

Bone growth stimulators are currently classified as Class III devices, they are subject to premarket approval prior to marketing. As background, devices that were not introduced into interstate commerce for commercial distribution prior to the original Medical Device Amendments on May 28, 1976 are considered post-amendment devices. If they have not been found substantially equivalent to a device placed in commercial distribution after that date or reclassified, they are automatically classified as Class III devices. Bone growth stimulators fell within this requirement.

There are two types of bone growth stimulator devices: invasive or implantable, and noninvasive devices. Noninvasive devices are associated with product codes LOF and LPQ. FDA is proposing that only devices that fall within these two product codes be reclassified from Class III to Class II.

Implantable bone growth stimulator devices associated with product code LOE are not within the scope of this proposal as they present added risk compared to the noninvasive devices.

Noninvasive bone growth stimulators are externally applied. They typically utilize a generator and transducer to deliver electrical, magnetic or mechanical (ultrasonic) waveform to the fracture site to augment bone healing. These devices incorporate internal features to monitor the output of the waveform and delivery of treatment. There are embedded safety features such as visual and/or audible alarms to alert the user of improper device function. These devices are intended to be worn over cast, clothing or braces, but

may also incorporate select patient-contacting components such as transducers, lead wires, and the device outer casing.

From November 1976 to the present, FDA has approved six noninvasive bone growth stimulator devices that utilize one of these four modalities to deliver current or wave to the treatment or fracture site.

Within electrical stimulation there are three options. Capacitive coupling (CC) typically uses metal electrodes which are applied to the skin to deliver a current to the fracture site. Pulsed electromagnetic field (PEMF) which uses an external coil to generate a modulated electromagnetic field near the treatment site. Combined magnetic fields (CMF) also uses an external coil system that uses a combination of direct and alternating currents to produce both static and alternating magnetic fields. Aside from electrical stimulation, there is low-intensity pulsed ultrasound, also known as LIPUS, which uses ultrasonic waves that are pulsed at low intensity using an ultrasonic transducer.

These devices are intended to promote osteogenesis as an adjunct to primary treatments for fracture fixation and spinal fusion or as a treatment for established nonunions or failed fusion. It's important to note that these devices are not intended to serve as the original primary means for promoting fracture healing or bone fusion.

FDA has approved bone growth stimulator devices under the following general category of indications:

- Treatment of an established nonunion secondary to trauma
- Adjunctive treatment of certain fresh fractures
- Treatment of congenital pseudarthrosis
- As an adjunct to cervical fusion surgery in patients at high risk for non-fusion
- As an adjunct to lumbar spinal fusion surgery at one to two levels

I will take the next few minutes to discuss why FDA has proposed to reclassify the

noninvasive bone growth stimulators.

As part of CDRH's 2014-2015 strategic priority "Strike the Right Balance Between Premarket and Postmarket Data Collection," we conducted a retrospective review of all PMA devices with active PMAs approved prior to 2010 to determine whether certain devices could be reclassified based on our current understanding of the technology. As part of this evaluation, noninvasive bone growth stimulator devices were identified as a potential candidate for reclassification. This proposal was published in the *Federal Register* on April 29, 2015.

In addition, we have approved six PMA devices. These devices have been on the market for a substantially long time for us to collect information on their safety and effectiveness. We also factored in the knowledge that we have gained from the FDA 2006 reclassification panel meeting, specifically, the risk mitigation strategies to move forward with this current reclassification proposal. FDA's rationale for doing so is also detailed in the proposed order to reclassify noninvasive bone growth stimulators into Class II (special controls). This proposed order was issued on August 17, 2020 and is available at the link shown there. Comments on the proposed order can be submitted through October 16, 2020.

As background, on February 9, 2005, FDA received a reclassification petition from RS Medical Corporation, hereon denoted as the Petitioner, requesting FDA to reclassify certain noninvasive bone growth stimulators from Class III to Class II. This request resulted in the June 2nd, 2006 panel meeting. The Panel reviewed information from the Petitioner. As part of the discussion, the Panel identified the potential risks to health as electric shock, burn, skin irritation and/or allergic reaction, inconsistent or ineffective treatment, adverse interaction with electrical implants and internal or external fixation devices, and biological risk. The Panel acknowledged that the Petitioner provided sufficient information to develop

special controls for most of these identified risks.

However, there was insufficient information provided to control for the risk of inconsistent or ineffective treatment due to lack of knowledge about how waveform characteristics such as pulse duration, amplitude, power, frequency, and potential modifications to the device affect the clinical response to treatment.

The Panel recommended additional clinical data or special controls to address the risk of inconsistent or ineffective treatment. As adequate special controls addressing the need for clinical evidence were not devised by the Petitioner, the Panel recommended retaining the classification of these devices under Class III. FDA concurred with this recommendation, as we had concerns with the Petitioner's proposed special controls to control for the risk of inconsistent or ineffective treatment.

Since that time, FDA has considered the outcome of the 2006 Panel and analyzed available clinical data since the panel meeting, including information available in the Summary of Safety and Effectiveness Documents, or SSEDs, for the six approved PMA devices available for consideration of the data to support reclassification under Section 520(h)(4) of the Food, Drug, and Cosmetic Act.

FDA also evaluated postmarket recalls and medical device reporting, or MDR, data to establish that there is probable benefit from the use of the device, assist with identification of the risk, and confirm that the risk to health is low.

Of note, the Panel did not identify risk with the ultrasound-based bone growth stimulator devices as they were outside the scope of the petition. However, based on our review of information, the risks identified with the ultrasound-based devices, along with their benefit, are comparable to those of noninvasive bone growth stimulators incorporating other modalities. The details of our analysis of the SSEDs, recalls, and MDRs will be discussed in the later slides.

Based on the totality of the evidence available since the 2006 Panel, FDA is proposing that sufficient information exists to establish special controls that together with general controls can provide a reasonable assurance of safety and effectiveness of noninvasive bone growth stimulator devices. FDA proposes that clinical data will be required to address the risk of inconsistent or ineffective treatment concerns raised in the 2006 Panel.

Sponsors will have the flexibility to develop their study design and assess the level of evidence needed to address certain parameters such as intended use, treatment population, and technological characteristics of their device. We will elaborate on the special controls in the later part of today's presentation.

I would now like to hand it over to Dr. Philip Belmont. Thank you.

DR. BELMONT: My name is Philip Belmont, medical officer in the Knee Arthroplasty Devices Team, Division of Arthroplasty in the Office of Health Technology 6: Office of Orthopedic Devices. I will cover an overview of the clinical information for noninvasive bone growth stimulators.

There are currently nine premarket approval PMA application-approved bone growth stimulator devices. The six original PMA applications included three pulsed electromagnetic field devices, one capacitive coupling, one combined magnetic field device, and one low-intensity pulsed ultrasound-based device. The SpinaLogic, SpinalPak, and SpinalStim devices were not part of the original PMA submissions but were added in later supplements. These devices included indications for a range of anatomical locations including lumbar and cervical spine, as well as the long and small bones of the appendicular system.

Under Section 520(h)(4) of the Federal Food, Drug, and Cosmetic Act, the FDA is granted authority to use clinical or other information from a PMA application that is more

than 6 years old but approved after November 28th, 1990, in the classification or reclassification of another device or to develop special controls.

There are three bone growth stimulator PMA devices which have available Summary of Safety and Effective Documents (SSEDs) which include clinical data that can be utilized under this rule. These include the CervicalStim cervical fusion system, the SpinalPak fusion stimulator, and the SpinaLogic bone growth stimulator devices.

The SSED information for P030034, the CervicalStim device utilized the same technology and design as that of the Physio-Stim bone growth stimulator. The CervicalStim clinical study was a randomized controlled blinded study of 323 high-risk adult subjects with evidence of compressed cervical nerve roots in symptomatic radiculopathy. The fusion procedure must have been either multi-level or the subject was a one-pack-a-day or more smoker to be classified as high risk.

There were 160 subjects in the control group receiving standard treatment consisting of an interior cervical discectomy and fusion, and an interior cervical plate. The treatment group totaled 163 subjects and consisted of a standard treatment plus prescribed use of the CervicalStim device which was intended to be worn for 4 hours per day for 3 months or until fusion occurred. Final follow up for both the control and the treatment groups was 12 months.

The primary effectiveness endpoint was the increase in frequency of cervical fusion success by 6 months postoperatively as assessed by radiographic evidence. Radiographic fusion success was defined as greater than or equal to 50% bony bridging on both the superior and inferior graft interfaces between adjacent vertebral bodies and less than or equal to four degrees angulation between adjacent fused vertebrae on flexion extension lateral films in the absence of radiolucency. At the 6-month time point, 102 of the 122 evaluable subjects representing 84% in the CervicalStim treatment group were judged to be

fused versus 81 of the 118 evaluable subjects representing 69% in the control group with a p-value of 0.0065. At 12-month follow-up, there was no statistical difference with respect to radiographic fusion with the CervicalStim reporting a 92.8% fusion rate and the control group reporting an 86.7% fusion rate.

The most common 6-month adverse event observed in the P030034 study are reported in this table. At 6 months, the number of subjects who experienced one or more adverse events was similar between the treatment and control groups. A total of 14 severe adverse events were reported in 13 subjects. None of the subjects were in the CervicalStim treatment group and five subjects were in the control group. These events included increased pain, shortness of breath, dizziness, unrelated trauma and injury, unrelated death, surgical complications, and adjacent level pathology. For the nine subjects in the CervicalStim treatment group, all severe adverse events were, in the judgment of the investigators, either definitely or probably unrelated to the device.

The SSED information for the SpinalPak fusion stimulator device utilized the same technology and design as the OrthoPak bone growth stimulator. The SpinalPak clinical study was a randomized controlled double-blinded study of 349 adult subjects. The objective of this study was to determine whether the SpinalPak fusion stimulator increased the frequency of overall success defined as the combination of both clinical and radiographic success when compared to placebo or inactive units after primary or first time one-level or two-level fusions within L3 to S1.

There were 172 subjects in the control group who received treatment with an inactive unit and 177 subjects in the treatment group. The SpinalPak fusion stimulator device was intended to be more continuously, except for periods of personal hygiene, until a physician had assessed overall success for a period of 12 months, which was final follow-up for both the control and treatment groups.

The primary effectiveness endpoint was overall success, which required an independent confirmation of both a radiographic successful outcome and a successful clinical outcome at final assessment.

Of the 349 subjects initially enrolled in the study and randomized, 83 patients withdrew from the study and another 45 patients were removed for protocol deviations leaving a core group of 215 patients.

At the final evaluation at the 12-month time point, 87 of the 110 evaluable subjects, representing 79% in the SpinalPak fusion stimulator treatment group achieved an overall success defined as independent confirmation of a radiographic successful outcome, and successful clinical outcome at final assessment versus 64 of the 105 evaluable subjects representing 61% in the control group with a p-value of 0.0018.

The most common adverse event observed in the P850022 Supplement 9 Summary of Safety and Effectiveness Document was skin irritation. Skin irritation was similarly observed between both groups with it occurring in five patients in the control group and four patients in the SpinalPak fusion stimulator treatment group. All other adverse events were single events with a similar occurrence profile between the two groups with seven occurring in the control group and four occurring in the SpinalPak fusion stimulator treatment group.

The SSED information for the SpinaLogic noninvasive bone growth stimulator utilized the same technological features and treatment signal as the Orthologic bone growth stimulator, P910066. The SpinaLogic clinical study was a prospective, randomized, double-masked, placebo-controlled study of 243 adult subjects. The objective of this study was to investigate the safety and effectiveness of the SpinaLogic as an adjunct to spinal fusion. Of the 243 patients in the intent-to-treat population, there were 125 subjects in the control group who received treatment within an inactive unit and 118 subjects in the treatment

group.

The SpinaLogic fusion stimulator device was dispensed within 30 days following lumbar fusion surgery, used for 30 minutes per day according to the instructions in the patient manual, and used for 9 months. Of the 243 patients in the intent-to-treat population, 42 patients withdrew from the study, died or were removed for protocol deviations, leaving 201 evaluable patients.

The primary endpoint for the determination of effectiveness was the status of radiographic lumbar fusion after 9 months of treatment as judged by a panel of evaluators. The assessment of radiographic fusion was a combination of the rating assigned by the investigator.

The SSED information for the SpinaLogic noninvasive bone growth stimulator utilized the same technological features and treatment signal as the Orthologic bone growth stimulator, P910066.

The SpinaLogic clinical study was a prospective, randomized, double-masked, placebo-controlled study of 243 adult subjects. The objective of this study was to investigate the safety and effectiveness of the SpinaLogic as an adjunct to spinal fusion. Of the 243 patients in the intent-to-treat population, there were 125 subjects in the control group who received treatment within an inactive unit and 118 subjects in the treatment group.

The SpinaLogic fusion stimulator device was dispensed within 30 days following lumbar fusion surgery, used for 30 minutes per day according to the instructions in the patient manual, and used for 9 months. Of the 243 patients in the intent-to-treat population, 42 patients withdrew from the study, died or were removed for protocol deviations, leaving 201 evaluable patients.

The primary endpoint for the determination of effectiveness was the status of

radiographic lumbar fusion after 9 months of treatment as judged by a panel of evaluators. The assessment of radiographic fusion was a combination of the rating assigned by the investigator, masked or treating orthopedic surgeon, and two independent masked reviewers that included a musculoskeletal radiologist and an orthopedic surgeon. The independent orthopedic surgeon utilized all radiographic imaging like the other two reviewers but additionally had patient-level clinical and surgical information to aid in lumbar fusion assessment.

At the final evaluation at the 9-month time point, 67 of the evaluable subjects, representing 64% in the treatment group, achieved an overall success versus 42 of the evaluable subjects, representing 43% in the control group, with a p-value of 0.03.

Masked treating orthopedic surgeon and two independent masked reviewers that included a musculoskeletal radiologist and an orthopedic surgeon. The independent orthopedic surgeon utilized all radiographic imaging like the other two reviewers but additionally had patient-level clinical and surgical information to aid in lumbar fusion assessment.

At the final evaluation at the 9-month time point, 67 of the evaluable subjects, representing 64% in the treatment group, achieved an overall success versus 42 of the evaluable subjects, representing 43% in the control group, with a p-value of 0.03.

In conclusion, based on the clinical data available in the three premarket application Summary of Safety and Effectiveness Documents that were reviewed, the noninvasive bone growth stimulators all demonstrated a clinical benefit. Additionally, the adverse event rates for the bone growth stimulator devices were low and similar between the treatment and control groups.

Dr. Jesse Muir will follow me with his presentation.

DR. MUIR: Hello, my name is Jesse Muir. And for the final part of the FDA

presentation, I will provide an overview of available postmarket data, risks to health and mitigation, as well as the special controls that FDA is proposing for reclassification of bone growth stimulators to Class II.

While the Summary of Safety and Effectiveness Documents discussed show a low adverse event rate and no sign of serious device-related adverse events, FDA conducted an additional review of available postmarket data including a review of published literature.

Prior to the 2006 bone growth stimulator reclassification panel was a long history of published studies on the potential of bone growth stimulator devices and most of these studies were published on in vitro or animal in vivo data. There was some information on clinical use of the device, including studies by Dwyer and Becker in the 1970s that showed that bone growth stimulator devices may have a positive clinical effect when used in conjunction with spinal fusion.

Later published clinical studies in the 1990s found a wide range of efficacy of bone growth stimulator devices on fusion rates from 60 to 80%. These studies include diverse anatomical locations, inclusion criteria, and treatment devices, all of which may have affected the observed fusion rates.

Preclinical animal and in vitro studies are consistent with our literature showing a variability in the efficacy of treatment. Veronesi found that changes on the primary frequency of a PEMF treatment can significantly affect or even negate the therapeutic benefit of treatment. Zhang et. al demonstrated that in vitro the different EMF waveforms can have either pro- or anti-osteoblastic effects, and Galli similarly found that variations in the parameters of a delivered signal can affect the treatment efficacy. Overall, these studies show that changes in therapeutic signals in bone growth stimulator devices can have unpredictable effects on the efficacy of treatment. As the body of scientific evidence at the time does not allow for prediction of treatment efficacy based on signal waveform,

FDA's conclusion from the available data is that clinical data would be needed to demonstrate the efficacy of a therapeutic treatment of a bone growth stimulator device.

To further evaluate available clinical data, a comprehensive literature review was performed looking for published clinical studies of FDA-approved bone growth stimulator devices. After filtering for off-label use, a total of 14 clinical studies were identified. Of these, four included the use of a PEMF device, seven used a LIPUS device, and two used a closed magnetic field device. In combination, these studies included an analysis of over 10,000 subjects.

In terms of efficacy, the studies had a wide range of therapeutic treatment benefits ranging from 32.8 to 97.4%, which is consistent with the prior clinical animal in vitro published data showing a wide variety of efficacy components. It should be noted that only two of the studies were properly controlled, both of which did demonstrate an improved outcome in the treatment group relative to the control group.

Each study was evaluated to determine if any safety signals were present. Of the 10,000 subjects across 14 studies, only a single adverse event was reported. While the studies are not all specifically designed to assess adverse events, literature does not identify any significant safety concerns with use of bone growth stimulator devices.

An analysis of medical device reporting for the FDA was performed to evaluate the safety signals of bone growth stimulator devices. Across all approved devices, a total of 270 MDR reports were identified since 1984. The vast majority of adverse events identified in the MDR database are skin reaction, such as rashes and hives, which are likely device-related events. Based on a review of reported MDRs, these are due to reaction to the ultrasound gel for the LIPUS device or reaction to the electrodes for the closed capacitive device. Both of these devices include patient-contacting components. A small number of subjects had allergic or other reactions to ultrasound gel and electroadhesive. In MDRs

with follow-up reported, the skin reaction generally abated with cessation of using the device and/or topical treatment and did not have any long-term health effects. Most other events identified cannot clearly be determined to be device related.

Pain is the second most common event, although pain is expected at the fusion site, as are other events such as swelling and infection. Other events, such as cardiac issues, mass/tumors, and hospitalization could not be clearly linked to use of the device.

Overall, the rate of reported events is low and represents a tiny fraction of the patients treated with bone growth stimulator devices each year. This is consistent with data reported in the available SSEDs and literature.

A review of recalls for bone growth stimulator devices identified only two recalls, both Class II, that occurred in 2009 and 2010 due to an issue with a transducer component, both of which were resolved with no significant issues. No recalls raised any concerns regarding the general safety or efficacy of bone growth stimulator devices.

Based on the prior 2006 reclassification panel and the data available in SSEDs, literature, MDR and recall databases, the following risks related to bone growth stimulator devices have been identified and proposed mitigation methods are depicted here for each identified risk.

First, the failure or delay of osteogenesis has been identified, which would represent a lack of device efficacy. As there is not significant evidence that the efficacy of the device can be evaluated through nonclinical testing alone, FDA is recommending that clinical performance testing, nonclinical performance testing, software testing, and labeling all be included as mitigation methods in the special controls. Remaining risks can be mitigated through nonclinical testing and labeling. These include burns, electrical shock, electromagnetic interference, adverse tissue reaction, adverse interaction with internal and external fixation devices, and adverse biological effects.

As stated in previous slides, available data were assessed and the conclusion is that efficacy of bone growth stimulator devices cannot be demonstrated through nonclinical testing alone. As FDA does not believe that clinical effectiveness can be demonstrated through bench or animal testing, we are recommending that clinical performance testing be included as a special control. This special control is not intended to address safety of the device, which can be addressed through nonclinical performance testing special controls, which are on the following slides.

In addition to the clinical performance testing, nonclinical performance testing will be needed to demonstrate that the device can perform as intended under its anticipated conditions for use.

In order to help establish a full understanding of the device substantial equivalence determination in a future 510(k) application, characterization of the designed output signal should be included in any marketing application along with verification and validation that the designed output is reaching the intended treatment location. Thermal safety and thermal reliability testing should be provided to demonstrate that the device does not pose an increased risk of burns due to heating or transferred energy during treatment.

Additional validation that the therapeutic signals within safe physiological limits should be provided such as evaluation of the safety of induced currents or risk of complication due to the mechanical wave generated by ultrasonic devices.

Valuation of the use life of the device should be provided to demonstrate that the device signal did not change over the lifespan of the device and that expected wear and tear does not cause potential harm to the end user, such as due to a frayed wire. Further nonclinical testing includes biocompatibility evaluation of any patient-contacting components such as electrodes as well as electromagnetic compatibility and safety tests. Finally, labeling controls would include necessary labeling to allow for the safe and effective

use of the device.

I would like to conclude this presentation with the following FDA comments. A reasonable assurance of safety and effectiveness has been demonstrated for the FDA-approved devices listed within the proposed reclassification through the PMA process.

The scientific literature indicates that a small difference made to the general device type can cause a device to be ineffective. These differences may include an alteration of the treatment signal and associated treatment field.

The issue raised by the proposed reclassification is whether sufficient scientific knowledge exists to adequately define 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.

And assessing the risk profile for any device 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.

Based on the data discussed, FDA believes that the proposed special controls are sufficient to demonstrate the substantial equivalence of future bone growth stimulator devices.

DR. SMITH: Thank you to all the FDA panel presenters.

Prior to moving forward, there's one item from the last session. Due to a technical issue we did not have the opportunity to ask Dr. Osborn his opinion upon Question 3 and I'd like at this time to ask Dr. Osborn, for the record, his comments on Question 3 of the last session.

(Pause.)

DR. SMITH: Dr. Osborn has --

DR. OSBORN: I'm sorry. So I concur with the reclassification with the controls that

were mentioned for the facet screws, sorry.

DR. SMITH: Thank you, Dr. Osborn.

And again, thank you to all the FDA presenters. Are there any clarifying questions from the Panel?

Yes, Dr. Yang.

DR. YANG: Apologies, I have to unmute myself. I have two questions, actually, with regard to effectiveness, one that concerns the adjunctive use for cervical spine fusions and one for lumbar. So with regard to the CervicalStim, the SSED information P030034, can I just clarify that you said that there was a difference at 6 months with a p of about 0.006, I think you said, but at 12 months, I didn't hear that, the difference between 93% and 87% given no standard deviations and whether or not there was any significant difference between the two at that stage.

DR. BELMONT: This is Philip Belmont. At 12-month follow-up for the CervicalStim there was no statistical difference with respect to radiographic fusion with the subject device reporting a 92.8% fusion rate and the control group reporting an 86.7% fusion rate even though it was nominally increased.

DR. YANG: Okay, so no significant difference at 12 months --

DR. BELMONT: Correct.

DR. YANG: -- for that study, okay. Then the next one has to do with the lumbar, both of them, the SpinalPak and the SpinaLogic. For these two, I noticed that the outcome was not just radiographic function, but the outcome was radiographic function coupled with clinical function for at least one, if not several, of the assessors. So when they say clinical function, what does that -- what does that actually comprise? And how do you think that affects the fair judgment of outcome given that they're also looking at patients and not just a straight-up objective radiographic function?

DR. BELMONT: So I think it helps in the assessment because they also used a clinical evaluation endpoint. In the SSED, we do not know exactly what the clinical evaluation endpoint was, but the reviewers did have -- be able to review the clinical notes and also in addition to the radiographic outcomes. So it would be an improved assessment of the assessment of the subject device.

DR. YANG: Oh, improved but not standard? So they were using their clinical judgment rather than actual clinical surveys of any kind, any PROs or anything like that?

DR. BELMONT: Yes, from the SSED, that is my finding from that, yes.

DR. YANG: Okay. One last question. The dropout rate for the SpinalPak is concerning, 349 down to 215. So you very quickly mentioned it, I'm sure I missed it, but the primary reason for such a huge dropout rate for that study?

DR. BELMONT: I do not have -- I cannot tell you that from the SSE document.

DR. YANG: Okay, thank you.

DR. SMITH: Yes, Dr. Elder.

DR. ELDER: Ben Elder. All these studies were older and I just wanted to clarify what the instrumentation or fixation that was used in these studies was. For instance, in cervical it was anterior plating used and what were the posterior instrumentations used, because all the fusion rates were pretty well compared to some of the control groups from just interbody fusion with allograft from more recent FDA studies.

DR. MUIR: This is Jesse Muir. So there were a -- there's a difficulty in discussing what information we can share, it's only what is available in the SSED we're able to share for this Panel, but we do recognize the type of approach, for the surgical approach may affect the final success rates of anything, which is one reason why we do believe -- part of the reason we believe that clinical data would be needed to demonstrate effectiveness, especially using whatever the -- as techniques may change.

DR. SMITH: Dr. Finnegan.

DR. FINNEGAN: Maureen Finnegan. So a couple of questions. One is do we know if the industry rep put the electrodes on the patient and the patient just attached the stimulator or did the patient actually put the electrodes on themselves? That's question number one. And question number two for the FDA is are we talking just about bone stimulators for the spine or are we talking about bone stimulators for long bones, as well?

DR. MUIR: Hi, this is Jesse Muir again. Most of these devices are provided to the patients who then treat themselves at home, so the standard treatment for bone growth stimulators, the patients would be applying the electrodes on their own, it is more than a device that did not provide a signal was used for the control group subpopulation, pardon me.

And for the second -- for the second question, we are looking at all noninvasive bone growth stimulators, so this would include some devices that have indications for the spine as well as other devices that have indications for long bones.

DR. FINNEGAN: So another question was for the spinal studies you did, did they put the age of the patient and/or the educational level so we have some idea of if they were sophisticated or if, in fact, they were not sophisticated?

DR. MUIR: I can't speak on that particularly. Dr. Belmont, do you have any information on the age of the patients?

DR. BELMONT: I do not have any information specifically on the age of the patients in these studies.

DR. SMITH: Dr. Alander.

DR. ALANDER: Dirk Alander. I was curious, on these studies for assessing the spinal fusion, were these just plan radiographs or are we talking about CT scans? Dr. Belmont?

DR. MUIR: Dr. Belmont, you're muted.

DR. BELMONT: From the three studies they were all plain radiographs.

DR. ALANDER: Thank you.

DR. SMITH: Dr. Pfeffer.

DR. PFEFFER: I followed this literature a long time since I did research on this during my residency, and I have no question about the efficacy in terms of facilitating bone healing. My only concern is whether they work or not, whether any new devices are efficacious, I think that's our main concern here. Will a new device come on to the market and waste 3 months, precious months, of a patient's recovery with a device that doesn't work?

So I just have a general process question, I don't understand. What will be the difference between a true PMA for a new device versus what you're suggesting, which would be Class III, usually, versus what you're proposing, which would be Class II with special controls. What's the actual difference for a new product coming on the market once you say all of these are Class II?

DR. MUIR: Yeah, this is Jesse Muir. Thank you, that's actually an excellent question. So there's a lot of other regulatory processes between the Class II and Class III devices including postmarket follow-up, annual reporting, 30-day notices that are required for Class III, as well as premarketing inspections versus the regular inspection cycle for Class II devices. Class II devices would be covered under general controls which would regulate the design controls and any modifications made to the device and future 510(k)s needed for modifications for the device.

So we're looking at, and our proposal would be is that we would still need clinical data to demonstrate efficacy of the device due to questions on how any difference in the technology could affect efficacy. But these other types of controls that we have in place in the Class III based on the long history of these devices and our understanding of the safety,

we don't think this higher bar is needed for these devices at this point based on our understanding of the history, the very solid both literature, MDRs, etc. So we're looking at moving those towards the lower -- the general controls and the special controls in the Class II field.

DR. PFEFFER: So is it fair to say that for everything we're doing today, I mean, unless there's an exception, that the Class II designation would have no less-rigorous objectively controlled studies to pass FDA muster than a Class III? You know, there was the -- the data that you need to get from clinical studies will be equal to the Class III designation. It's just all of the other issues, the postmarket -- you know, all of the other things you mentioned that would be there. Is that fair to say? The rigor of the scientific study would have to be as -- would be equal to a Class III. For a new product.

MS. ALI: Yeah, if I may address that question. So it seems like, based on what Dr. Muir has shared, that we'll be asking similar type of data, so our end goal is to ensure that we have high confidence in the safety and effectiveness of these devices. So some of the information that we were not able to identify, risk mitigations in the previous panel based on that we're recommending clinical even under a premarket notification for this device type, so the major differences between the process for PMA versus 510(k) for this device type would be that we would be shifting some of the manufacturing burden on the sponsor and we would not be reviewing them as part of the premarket review process.

So the major benefit to that would be that we'll be able to provide faster access to these devices to our patient population. We recognize that each technology is different and the type of questions we may be asking may be different, but overall there is a lower bar for adjunctive device in terms of the type of questions we will be asking in a premarket review versus a premarket -- a PMA review versus premarket notification application.

DR. PFEFFER: I'm sorry to belabor this here, but the rigor of the academic work

that's needed, prospective randomized studies, will be equal for Class II as it will for Class III for FDA? We're all used -- as doctors, we're used to reading in the literature will be equivalent.

DR. MUIR: So our expectation is that we are looking at the same level of data to demonstrate efficacy of the device through a clinical study.

DR. PFEFFER: Thank you.

DR. MUIR: And I did want to clarify on a comment you made earlier, just a little bit of clarification between this section of the Panel and the other section, it's a little bit different. The other sections are unclassified devices that are -- we're trying to classify. This is a currently classified device that we're proposing to down-classify. It's a slight difference and I just wanted to clarify that.

DR. PFEFFER: Thank you very much.

MS. ALI: Yeah, just to add on to that, we'll be turning it back to the Panel members to comment on are there instances we should consider where we may look at literature reviews and limit the clinical burden.

DR. SMITH: Dr. Yang.

DR. YANG: To follow up on the question, though, as far as the difference, with a PMA, those are guided, are they not, by the FDA and primarily oversight of all that, whereas a 510(k) and a Class II would really put the burden on the sponsor to provide that information, is that correct?

DR. MUIR: Sorry, could you repeat the question?

DR. YANG: So with a Class III device, the PMA process has significant guidance by the FDA during the conduct of the studies, etc., etc. However, with a 510(k), meaning proving equivalence, the majority of the burden of providing similar data, if you want to say similarly rigorous data, is actually on the sponsor rather than a sort of primary oversight by

the FDA. Is that an appropriate statement or no?

DR. MUIR: So this Jesse Muir. I would not clarify it or I would not define it in those terms. So regardless of if we're looking at a PMA, 510(k), any type of device, any clinical study performed in the United States would require an IDE submission and we review those with the same rigor regardless of the marketing pathway for the device.

DR. YANG: So I guess my question is for Dr. Ali's statement, what then is the burden put on the sponsor versus -- for Class II versus a Class III, then? When you said that.

DR. MUIR: So manufacturing controls and a few of the other controls are things that will be put on the sponsor that are normally as part of a PMA, any manufacturing is part -- it requires FDA approval to make modifications, whereas manufacturing controls for Class II devices are more on the sponsor's side.

MS. ALI: And also reducing the need for both preapproval and post-approval inspections for the PMA process.

DR. PFEFFER: But Dr. Ali, we've all -- or Dr. Muir, I'm sure we've all read the letters that came with this issue regarding bone growth stimulators and the concern from certain physicians that this not be deregulated to a Class II because it would allow inferior devices with different modalities, different bone growth modalities, to appear on the market and not be efficacious, right? We've all seen those letters in our packet. I think it's a reasonable point if that, in fact, would happen, right?

But if FDA says no, that will not happen because any new device, even if we classify this as a II will have to have a rigorous, academic, prospective randomized study that FDA has required for PMAs to be submitted. I think I, as a doctor, and the Panel would say that's fine with me as long as FDA will prove with a high-level study the efficacy of the new device and its potential new parameters. That is, I think, the underlying issue for all of this, if anyone has another thought. You're assuring us that is the case, correct?

DR. MUIR: So, I mean, we definitely recognize the concern of will any new technologies be efficacious and we took that into consideration when drafting our proposed special controls in that we would need -- we would want to see clinical evidence that these devices are efficacious, absolutely, especially in the case of any new technologies.

DR. PFEFFER: Might you accept potentially less quality studies, like a study from Europe and -- that's been published in a journal that's not as highly respected as those that are in the United States as allowing a Class II? What level of evidence will you require? Because we've all seen things that the FDA has approved that perhaps hasn't had the highest level and there's a history of some of that, although I've been very impressed with FDA's process, which is why I'm asking for details.

DR. MUIR: And it's very hard for us to say exactly what we'd see in what companies submit in the future. You know, as part of FDA, we do look at the least burdensome approach for data. We are expecting the same rigor and quality of data for a submission. It may depend on comfort with technologies as things progress. However, at this stage, with having the clinical data as a special control, we would be expecting quality clinical data. You know, a poorly designed study that doesn't answer the questions would not address our concerns regarding the efficacy of the device.

DR. SMITH: Mr. O'Brien.

MR. O'BRIEN: Yes, I agree with the line of what Dr. Pfeffer's saying, for sure. I have the same concerns, only perhaps from a different perspective, but it seems to me, rather than clarifying questions, we're moving ahead to the discussion of the questions itself because ultimately, as a patient, it seems to me that delay of osteogenesis, pseudarthrosis in spine is an adverse event that is extremely important and we're discussing it, the need to put in a special control, sort of tells me that it almost fits the definition that it has to be Class III. When you look at the definition of Class III in terms of substantial importance to

preventing impairment of health, that is an important issue. I don't -- you know, it almost seems to me that by itself, de facto, the fact that we're discussing it at this level and the need for special controls tells us that's where we're at and we really should keep it where it is.

DR. PFEFFER: This will come up throughout the day, I think, the next 2 days. That's why it's important perhaps to -- Dr. Smith, to clarify this for all of us now.

DR. SMITH: There's a few pending questions I'd like to address.

Ms. Bonnell, you've been waiting for some time.

MS. BONNELL: Sure, thank you. Stacey Bonnell, non-voting Industry Rep. So I appreciate the dialogue and the concern. It's my understanding, and I just wanted to clarify maybe Shumaya's earlier comments in that I believe that the Agency's recommendation would be down-classification to Class II, which would require a 510(k) premarket notification with clinical. And so that clinical would require an IDE in advance and that IDE need not be prospective randomized, as Dr. Pfeffer, you had asked that question in terms of Tier 1 evidence, but that clinical evidence can be met in other ways but not with diminished rigor. I think that that's important to make that distinction. So I hope that that adds some clarity there.

DR. PFEFFER: What rigor is there if not a -- I've been on the FDA for however long, you guys know, 12 years, 14 years. The most rigorous studies are those that are presented as prospective randomized studies. Even those, as we all know, have their weaknesses. So what could possibly supplant a prospective randomized study for a new device that could destroy someone's life if it's not efficacious, i.e., a bone growth stimulator that's on for 3 months when someone's going nowhere with it? How depressing.

DR. MUIR: So just to -- this is Jesse Muir from FDA. Just a comment on a few things here. For PMA devices, there is no -- necessarily a requirement for a prospective

randomized clinical study. What we look for is valid clinical evidence and this could include OUS clinical studies even for novel PMA devices. This could include, obviously, randomized controlled studies, this could include PRO data, registry data, there's a lot -- we look at a large volume of valid scientific evidence even for PMA devices, and what we're talking of is using the same rigor we would expect from the PMA for the clinical in this case.

DR. PFEFFER: Good. Thank you, thank you.

DR. SMITH: Dr. Gilbert, you've been waiting for some time.

DR. GILBERT: Yes, Jeremy Gilbert. So I just have a question about mitigation method and would a postmarket surveillance study constitute a potential mitigation method? So you do the clinical data beforehand, before you get the 510(k) approval, but could you then also say you need to follow patients after approval for some period of time to assure that it works out in the real world as it did in the clinical performance data study? So postmarket surveillance, is that a mitigation method that's acceptable?

DR. MUIR: So this is Jesse Muir from the FDA again. That is absolutely something we look at, and we have been looking at for many devices recently. It would not be something we would necessarily include as a special control as needed, but for any device type, a 510(k) or PMA or de novo, if there are uncertainties or questions that cannot be answered with the clinical data, postmarket data is something that we do consider.

DR. GILBERT: That's something really this Panel could consider as an additional mitigation method at this point and deliberate.

DR. MUIR: Yeah, it can be discussed, of course.

DR. SMITH: Dr. Ebramzadeh.

(Pause.)

DR. SMITH: Excuse me, sir, I believe that your microphone is muted.

DR. EBRAMZADEH: Sorry about that. Eddie Ebramzadeh from UCLA. I want to go

back to the presentation of the literature on CervicalStim in particular, and even though the fusion rate was impressively higher in the treatment group and in the control group, the adverse events were higher in the treatment group, in particular increased neck pain and shoulder or arm pain. I understand these may not be statistically significant, but I'm just curious if the Panel has any comments on -- it's just a curious trend. Several of the -- several other, even, of the adverse events are higher in the treatment group and I just thought that was inconsistent with the fusion rates being higher, so if anybody has any comments about that, I'd be curious. I think it relates to what we're discussing as far as the risks and all that.

DR. PRICE: This is Amy Price. I was wondering about that, also, but then I also wondered if it's perhaps because they're fusing properly, they're healing faster and they may be getting active more quickly than they normally would, because I also noticed the events for increased injury and other things also went up which seemed to be kind of relative to increased activity.

DR. EBRAMZADEH: That's a very good point. Thank you.

DR. SMITH: Are there any other comments?

Yes, Dr. Finnegan.

DR. FINNEGAN: Maureen Finnegan. I hate to be a spoiler, but having used these a lot in long bone trauma, these are patients who usually are frequently uneducated. Some of the devices do have "compliance," but all they do is measure whether the machine's been turned on or not. And so I think that given the results that they have produced with a patient population that probably is not as rigorous as people would like, would suggest that they are very safe and I don't think anyone really understands the efficacy, but they certainly are safe.

DR. SMITH: Are there any additional comments?

Yes, Dr. Alander.

DR. ALANDER: Yeah, thank you. Dirk Alander. I think that my big concern is just making sure that the efficacy is going to be assured the best we can if this was downgraded to a Class II.

DR. SMITH: I would like to ask a question, if I may. In reviewing the literature that was summarized very nicely, there appears still to be a lot of questions about how efficacy is defined and I think all of us would agree -- I believe would agree that when defined is when you have a solid spine fusion. It's something where the goalpost has moved over the years and we're still struggling with that, and particularly with modern spinal instrumentation nonunions frequently don't present until a year or even more after surgery.

Some of the studies of the existing devices, we're assessing fusion off radiographs and surgeon opinion at 9 months and it seems -- there seems to be more concern about efficacy than safety, but a question, if you could give us your opinions regarding how does one define a fusion? And then are we going to define fusion and efficacy for new devices to a higher standard because we now probably have higher standards in the literature to define a fusion? Or will the newer devices be asked to define fusion to the same standards as the already approved devices?

DR. ALANDER: Okay, can I --

DR. SMITH: Yes, Dr. Alander.

DR. ALANDER: Dirk Alander. That kind of goes to my question about CT scans. These were prospective studies and it would've been nice to have a CT scan because I think in spine, specifically, it is very hard to ascertain a fusion. You can look at measurements of opening of the spinous processes and you can look at what you think is a solid fusion at a year, and they'll be back in a year and a half or 2 years with a pseudarthrosis. So to my

mind, a CT scan is much more valuable, at least than looking over plain radiographs. And I do think we have to hold -- we have to use newer techniques to validate a true fusion. It is tough, but I think a CT scan in a prospective study would've been much more valuable, to me.

DR. SMITH: Dr. Ebramzadeh.

DR. EBRAMZADEH: Yes, thank you. Eddie Ebramzadeh from UCLA again. The way I was introduced to this a couple decades ago was that it was more of a salvage procedure and not so much to prove efficacy, but if it didn't offer any substantial risk, then it was a good thing to try. But now we are discussing, what I'm hearing is more an expectation of efficacy and I'm wondering if the newer technologies or newer devices are going to be held to a higher standard because of the expectation and if so, we should be clear about that and not pretend like they're going through the same process of testing.

DR. SMITH: Yes, comments from the FDA.

DR. MUIR: Hi, this is Jesse Muir from FDA. I wanted to try to comment both to Dr. -- both the last two. For the first comment, you know, I think we did definitely agree, the difficulty of assessing fusion rates is an ongoing and always evolving process. If we saw a company came in with an IDE and are using our current standards, we would probably be hoping to see CT data, but most of these studies that we're discussing are much older studies performed in the '90s or earlier where we looked at -- generally, these were all clean radiographs.

You know, we'd always hope to see the most modern and gold standard techniques for assessing things and, as with any Class III device, PMA device, that changes with time and we would evolve with the technologies to hopefully keep looking at the best process because we want to demonstrate that these devices are effective, that is the absolute -- as well as safe, of course, but that is a lot of the questions, obviously, we're discussing here.

I'm sorry, I'm now blanking on what the second question was. Could you repeat your comment, the second comment?

DR. EBRAMZADEH: Thank you. That earlier in the history that this was, at least in my perspective, considered this as salvage sort of procedure for patients who had really not much to lose, they had a nonunion that was -- that they had tried many other things and so as long as it didn't produce any substantial risk, it was a good thing to try. Now we're expecting efficacy and if efficacy is not shown according to the documentation that we're going to see later and so on, that that in itself produces a risk that if it's not effective and producing union, but that's a different perspective from if it doesn't hurt, let's try it. So I want to know what our perspective is today, whether if it doesn't produce risk it would be acceptable to move on with classifying it as Class II and so on.

DR. MUIR: So yes, that is an excellent point and so what we're looking at is -- in our consideration here is the labeling and the indications for use of the devices. These devices each have a specific indications for use and should these fall into a Class II regulation to demonstrate substantial equivalence, they would have to demonstrate that they are safe and effective with the same indications for use. If they were to change indications for use, they would need clinical data to support those different indications, just like any other -- if it fell into the Class III regulation.

So the devices that are currently on the market do have a slight variation in the indications for use, but most of them generally are, as you commented, for failed unions or existing nonunions, that's going to be established at some time post-fracture. With that, you know, what we're considering now would be to continue to review those in that context unless new clinical data was provided to demonstrate others, other intended uses, but we would be wanting -- even in the case of the existing devices, we did look at efficacy but we were looking at efficacy of treating an existing nonunion or treating a failed union at

that time point. So efficacy has always and will always be an endpoint that we are considering for these devices.

DR. ALANDER: Me? Dirk Alander.

DR. SMITH: Yes, I'm sorry. My microphone was off. Yes, Dr. Alander.

DR. ALANDER: I think this -- I might be off here, but Eddie, I think you bring up a good point. That's how I learned how to use them and wait for -- you know, do your best and if a nonunion is developing, I think that the -- especially in spine, this is the marketing and the deployment of these devices has changed. It's saying okay, we have a high-risk patient, we're just going -- we're going to put it on you now, early, and then we'll have a better result. And so it's not waiting for that pseudarthrosis to develop, it's let's put it on now.

And so I think that the way that they're being used is different and so that, in my mind, makes the efficacy much more important. So if you take a device that costs a couple thousand dollars and you want to have this person wear it, and that's not early on in a fusion and you better be pretty sure that they're going to be getting a good benefit from it. And so I think the shift, there's been a shift in how they're using it and I think that's why efficacy is much more important now.

DR. SMITH: Dr. Yang.

DR. YANG: So along those same lines, we all -- it sounds like we're all not so confident about effectiveness. So to go off something Dr. Finnegan said, you know, we're talking the indications right now, primary versus adjunctive, the only data that you guys have presented has been adjunctive, at least that I could see, on those studies, the spine fusion. Can the FDA, maybe after lunch, summarize for us a little bit about appendicular issues and also where it's being used as a primary treatment? So in other words, more evidence for effectiveness, particularly in the appendicular field because I don't see or I

haven't seen anything on that.

DR. MUIR: I can comment really quickly in that the appendicular devices are generally also indicated as adjunctive to primary fixation either for testing plates, external fixators or however primary fixation is achieved.

DR. YANG: Do you have any data to present to us about that?

DR. MUIR: The data for those are not available due to the SSEDs for those being too old. We are not able to utilize that data. Literature, some of the literature cited in our literature review did include studies of the long appendicular -- appendicular system studies, but those were literature based, so not FDA-approved clinical studies, but in similar -- showing similar effectiveness that we had seen in the SSEDs and other data.

DR. SMITH: Are there any other comments?

(No response.)

DR. SMITH: Are there any other comments?

(No response.)

DR. SMITH: If there are no other comments, at this time we will break for lunch. We will reconvene at exactly 12:15 p.m. At that time we will convene with our second open public hearing and continue with Panel deliberations and FDA questions.

(Whereupon, at 11:07 a.m. a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(12:15 p.m.)

DR. SMITH: We will now proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel to present data, information or views relevant to the meeting agenda. Mr. Swink will now read the Open Public Hearing Disclosure Process Statement.

MR. SWINK: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency during this Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationships that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. Thank you.

DR. SMITH: There have been several requests to address the Panel for this session. Our first speaker will be Charles Sansur, M.D., who is Director of Spine Surgery at the Department of Neurosurgery at the University of Maryland School of Medicine.

DR. SANSUR: Hi. Can everybody hear me?

(No audible response.)

DR. SANSUR: Okay. And do you have my slides or should I share my screen?

(No audible response.)

DR. SANSUR: I can share my screen. Okay, there it is. Okay. So yeah, I'm Dr. Sansur. I'm the Director of Spine Surgery at the University of Maryland and I'm here on behalf of the AANS and CNS. Personally, I do receive royalties from Stryker for the development of the thoracolumbar fixation system, but I don't think that has a significant bearing on this topic with regard to bone growth stimulators. So I can go ahead and proceed to the next slide.

So bone growth stimulators, I have essentially two -- there are essentially three main types of bone growth stimulators, and we'll start out with our experience and knowledge of the transcutaneous devices. The transcutaneous devices are basically external devices. They take two forms. One is what we could classify as a pulsing electromagnetic field. The other one is a capacitive coupling type of device.

For the pulsing electromagnetic field, the patient wears essentially an external brace and this brace is also accompanied by a generator of an electromagnetic field. The patients wear these braces for several months after surgery, and we have studies such as is the case with Linovitz and Mooney, where the use of these external pulsing electromagnetic devices had resulted in improved outcomes and improved bone healing.

Capacitive coupling is another transcutaneous device with surface electrodes that are applied to the skin and an electric field is generated by applying a current between these surface electrodes, and there's prior evidence from Goodwin et al. of improved outcomes as a result of capacitive coupling.

In my practice, I have seen and witnessed the use of both and I have never really encountered any complications from these devices, and patients seem to tolerate them well and patients are happy to use them. Very rarely do I ever have a patient that gets one and feels that it's a problem. If we can go on to the next slide.

So bone growth stimulators, in addition to being external, they can also be internal and essentially what happens is during the time of the surgical fusion, a generator and wires are implanted. The generator serves as the anode and the wires serve as the cathode, and the current that is created through this process results in a usually solid and robust fusion. These devices may or may not be removed after the fusion becomes solid.

The potential complications with these devices are fairly minimal. However, as is the case with anything, infection could occur and there are times where I've gone back in on patients who have had these devices inserted and the fusion is very solid and robust, and at that time we remove the generator and do the surgery that we intend to do, and when we're doing the revision surgeries. I found these, the implantation of these devices, to be very straightforward and safe, and the removal of the generators to be very easy and simple.

All in all, on behalf of the AANS, we feel that it is appropriate for reclassification to Class II and if you have any questions, I'd be happy to answer them.

DR. SMITH: Thank you.

Our next presenter is Dr. Robert Muratore from Acoustic Sciences Association LLC.

DR. MURATORE: Hello, this is Robert Muratore speaking. I'm chief scientific officer of Acoustic Sciences Associates. On behalf of my colleagues, we thank Mr. Garcia and the Medical Devices Advisory Committee for this opportunity to address the Orthopaedic and Rehabilitation Devices Panel on the subject of the reclassification of noninvasive bone growth stimulators as Class II medical devices. We support the proposed reclassification of low intensity pulse ultrasound, that is LIPUS, noninvasive bone growth stimulators as Class II medical devices and propose a set of special safety and efficacy controls for validating 510(k) equivalence. Our response is limited to LIPUS devices and our opinions are based on our understanding of the science that underlies this technology.

In 1990, building on work by Duarte, Pilla and coworkers established the efficacy of ultrasonic stimulation for enhanced bone fracture healing. Ongoing research has shown that a LIPUS signal enhances soft callous mineralization in the early stages of bone fracture healing and increases hard callous strength in the re-mineralization and remodeling stages.

In bone, osteocytes maintain the protein and mineral content of the surrounding extracellular matrix. Lefkowitz and others found that mechanical stimulus is transferred across the plasma membrane of the osteocytes to the cytoskeleton via integrin protein linkages. Ultrasonic waves trigger an integrin response which in turn initiates a cascade of intracellular events.

Published research on molecular mechanisms has shown that LIPUS insonification enhances the production of COX-2, an enzyme in the production of prostaglandin PGE2, which in turn increases vascularity in the inflammatory and soft callous stages. This stimulates differentiation of osteoprogenitor cells to osteoblasts, thereby accelerating hard callous remodeling and cortical bone formation in the final stages of the bone fracture repair process.

The medical community now has a greater understanding of the utility of LIPUS for the treatment of fresh fractures at risk and delayed and nonunion fractures in patients. After more than two and a half decades of clinical use, it can be confidently stated that the application of a LIPUS signal for bone growth stimulation poses little or no risk of danger to humans.

A LIPUS signal is defined by several spatial temporal parameters, including the spatial average and temporal average acoustic power, I_{SATA}, the transmit carrier frequency, the modulation envelope, the period, the duty cycle, the effective radiation area of the acoustic transducer, and the control of acoustic propagation modes. Selection of these parameters depends on the characteristics of the propagating medium.

The critical non-thermal effects of ultrasound on tissue are cavitation and associated acoustic streaming and acoustic caustics. Cavitation bubbles can form in response to high-amplitude and low-frequency ultrasound pressure waves and lead to localized streaming and severe pressure changes upon collapse. Therefore, a metric such as the mechanical index (MI) is required to assure that acoustic pressure does not exceed the threshold for causing cavitation and potentially causing tissue damage. An acceptable value for MI in the output display standard is less than 0.7. Published test results indicate that the likelihood of adverse nonthermal biological effects is effectively zero if the MI is less than 0.5.

Acoustic caustics are counted by the beam nonuniformity ratio (BNR) defined as the maximum intensity divided by the average intensity with suitably precise determinations of intensity and position. To avoid generating acoustic caustics or hotspots in biological tissue, the BNR for therapeutic devices must be less than 8.0.

In order to demonstrate 510(k) equivalence with respect to device safety, we believe a potential vendor must show that the spatial average, the temporal average intensity, I_{SATA}, and the RMS acoustic power of a LIPUS signal will not produce deleterious biological effects.

Specifically, we recommend the following additional special controls for safe clinical treatment with diagnostic and therapeutic ultrasound: a mechanical index less than 0.5 and a beam nonuniformity ratio of less than 8.0.

In order to demonstrate 510(k) equivalence with respect to device efficacy, we believe that a candidate device must have particular signal parameters and must respect a well-defined set of contraindications.

We return now to a consideration of the LIPUS signal parameters that are effective in promoting bone growth. The acoustic power must be sufficient to overcome attenuation in the tissue pathway between the transducer located on the skin surface and the fracture

site. The pulse repetition frequency must be in a biologically relevant range on the order of a kilohertz and the carrier wavelength must be smaller than a fracture wave, which implies a frequency in the megahertz range.

Over the past 26 years, a wealth of literature has established the effectiveness of LIPUS subject to some contraindications. LIPUS has not been proven effective for other than long bone and small bone fractures. Chronic NSAID use inhibits COX-2 and the subsequent pathways that enhance fracture healing. LIPUS has not been shown to be particularly effective in overcoming this mechanism.

We believe noninvasive bone growth stimulators based on LIPUS fit the definition of an FDA Class II device in that the FDA general controls for medical devices would, by themselves, be insufficient to provide reasonable assurance of safety and efficacy.

However, LIPUS bone growth stimulators should not be considered Class III devices for the following reasons:

- These devices do not sustain or support life in the same way as more advanced medical devices such as pacemakers.
- They are not implanted inside the body and are used externally.
- Relying on ultrasound at diagnostic levels, they do not present an unreasonable risk of illness or injury.
- They have been demonstrated safe by 26 years of clinical use.
- These devices are designed for use on the bones in the limbs and therefore the ultrasound signal does not traverse any organs.

Requiring a clinical trial driven premarket approval pathway for these devices places an unreasonable cost and burden on innovation and has had a dampening effect on technical advancement and competition in this space to the detriment of the public. A reasonable set of special controls as proposed above could entirely mitigate any additional

risks that are not mitigated by the general controls.

Therefore, we support the proposed reclassification of LIPUS noninvasive bone growth stimulators as Class II medical devices under the 510(k) equivalence guidelines presented here. Thank you for your consideration.

DR. SMITH: Our final presentation is given by the Bone Growth Stimulator Coalition comprised of Bioventus, DJO Global, Orthofix Medical, and Zimmer Biomet. Dr. James Ryaby will be the first presenter for the coalition.

DR. RYABY: Good afternoon, everyone. I would like to thank the Panel and FDA for giving this opportunity for us to present today. The BGS Coalition is an informal group of manufacturers of the FDA-approved bone growth stimulators. The companies are Bioventus, DJO Global, Orthofix Medical, and Zimmer Biomet. The BGS Coalition supports maintenance of BGS devices in Class III.

The Panel should appreciate that reclassification would permit potentially ineffective devices to enter the market. BGS devices require control by Class III and an ineffective device would pose a serious harm to vulnerable patients.

Our speakers today are Dr. Mohit Bhandari, Dr. Chi Lim, and myself. I will talk about the regulatory considerations that preclude BGS reclassification; Dr. Bhandari will talk about evidence-based medicine; and Dr. Lim will talk about his experience with BGS devices in spine applications.

To tell you a little bit about myself, I had worked on BGS technologies for the last 30-plus years and currently I served as chief scientific advisor to Orthofix Medical.

The Panel should recognize that there are key regulatory requirements for reclassification. Any device to be reclassified must constitute a generic type of device that does not differ significantly in any feature related to safety and effectiveness. Also, there must be the ability to establish special controls which are based on nonproprietary, valid

scientific information again to assure safety and effectiveness.

Now, following the 2006 panel review, FDA and the Panel agreed that BGS do not meet reclassification requirements and no new evidence exists today in 2020 that changes this fact. Safety and effectiveness is only assured with these devices in Class III. Findings from the last panel review have not changed, we appreciate FDA's re-review of BGS status.

What was concluded in 2006 at the panel review was there was a lack of evidence to establish special controls, which would mitigate the risk of ineffective treatment. There was a lack of knowledge about how waveform characteristics affect the clinical response. There was a lack of knowledge about the impact of device modifications on the clinical response, and there was a lack of adequate preclinical test methods that would mitigate the risk of ineffective treatment. These findings are still applicable today, Class III remains the correct classification.

These devices are clearly not generic, there are different modalities, mechanisms, dosimetries, waveforms, designs, and intended uses, and all of these features directly impact safety and effectiveness. They're clearly not generic.

If you look at the device designs, as you can see in the photographs or if you look at the dosimetries, which range from 20 minutes a day to 10-plus hours a day, these are different devices. And I think the best demonstration of how different these devices are is to recognize that there are three separate technologies encompassed in BGS devices.

So at the top panel we have the pulsed ultrasound device, so that's a pulsed acoustic wave. The two middle technologies are both based on magnetic fields. The combined magnetic field technology, in fact, not only imposes an AC magnetic field, but it actually controls the DC magnetic field. Pulsed electromagnetic fields basically are rectangular waveforms that have specific rep rates and specific fundamental frequencies in the low kilohertz range, and then capacitively coupled fields directly apply an electric field to the

skin at a much higher carrier frequency. So these are very different waveforms, there's no doubt about it.

Modalities and designs, I've clearly shown you this. Dosimetries vary. And indications, all four of these devices share an indication for treatment of nonunion fractures. Only the pulsed ultrasound device has FDA approval for fresh fracture healing. The electrical and electromagnetic devices have indications in lumbar and cervical spine fusion.

Now, using ultrasound as an example, the top panel on the right shows an OUS pulsed ultrasound device and the bottom panel shows a U.S. PMA approved device, that of Bioventus. And you can see that the acoustic intensity, the acoustic field shape and size itself are very different and these are distinctly different waveforms.

Now, what we know is that these waveforms are very sensitive to any circuitry or component changes. So, for example, using ultrasound again, if we want to think about the output power or ultrasound field intensity, the frequency of the drive signal, the pulse modulation rate, the transducer size/shape, and acoustic matching layer material, as well as the fundamental piezoelectric material all affect the ultrasound signal that's generated. And I could go over these same issues for the electric and electromagnetic technologies, these same issues are present.

So any modification to a waveform can affect device safety and effectiveness, and FDA has so far recognized the need to review all proposed changes under Class III controls and, in fact, the Panel in 2006 concluded that "the lack of knowledge about how" these "waveform characteristics...affect the clinical response to treatment," and FDA agreed that "additional evidence...including preclinical test methods" would be "required to establish special controls." Today there is no new knowledge or preclinical methods to enable reclassification. In fact, newer studies highlight the continuing applicability of Class III

controls as seen in 2006.

So we have many examples where preclinical animal data did not translate into a positive clinical response. I'll use examples from pulsed electromagnetic fields. So there have been many studies published on acceleration of, for example, tibia fracture healing. However, clinically, when an over 200 patient double-blind, randomized, placebo controlled prospective study showed no difference in re-op rates in tibia fractures, there have been many publications on reversing OA in animal models. Recently, in an IDE feasibility study there was no benefit of PEMF compared to placebo as measured by WOMAC.

Using pulsed ultrasound as an example, there were high rates of spine fusion in rat and canine models but, in fact, another double-blind Level 1 randomized control study under an IDE showed no benefit of ultrasound compared to placebo. So we do not see straightforward translation of preclinical data to clinical effect.

We, as the coalition, strongly support IDE PMA pathway for all new devices and market entrants. Remember, member companies since 2007 and even before 2007 have made major investments in preclinical and clinical research that has been presented and published in peer-reviewed journals, and it's important to know that many IDE clinical trials have and are currently being conducted and only Class III ensures that this essential research will continue.

This information presented today demonstrates that Class III controls remain necessary for BGS devices. These multiple regulatory controls include substantiation of the effect of each new device by Level I or II clinical data, FDA review of all post-approval device modifications, and a comprehensive review by FDA of BGS manufacturing, including preapproval inspection and post-approval review of all changes. It's important to recognize that this set of controls is only available under Class III.

Level I and II clinical data are essential. The Panel and FDA in 2006 recognized that

there was a lack of adequate preclinical models. These knowledge gaps about how device parameters affect clinical performance still exist. The mechanisms of action vary across the different devices and are not completely understood. And as I've shown you, there are no scientifically validated preclinical tests that will predict BGS safety and effectiveness.

So current FDA reclassification proposal concurs that the risk of an ineffective BGS is clinically significant. However, there's a proposal that clinical data as a Class II special control would have flexibility in study design and the level of clinical evidence needed, we don't agree with this. We believe that Level I and II clinical evidence are required today for new BGS approval and the continuing need exists to have this high-quality data.

Recognize that Level I and II clinical evidence is standard in Class III but not in Class II. Class III requires proof that a device is safe and effective. In contrast, Class II devices are authorized based on substantial equivalence and no independent requirement of showing safety and effectiveness. Clinical data may thus be sought only in the extent to help safety and effectiveness.

And again, clinical data is not typically included in 510(k)s. However, when appropriate, as a special control, clinical data can include data other than randomized controlled studies such as partially controlled studies, studies without matched controls, case histories. In many cases, clinical data necessary to support a 510(k) may involve a relatively small number of patients with a simpler study design, clearly not the level of clinical data that would support a PMA. And for example, in pedicle screw systems that were reclassified to Level II, this was done with retrospective data and clinical literature, not Level I or II controlled studies.

So for BGS manufacturing, we believe that full PMA review of manufacturing process and changes is crucial to ensure consistent production of BGS with the appropriate waveform parameters. For example, each manufacturer relies on custom equipment in BGS

design and manufacture to precisely measure their proprietary waveforms and form the specifications unique to each BGS device. Premarket inspection of these processes is essential to provide safety and effectiveness. And the review of manufacturing and routine preapproval inspections are only found with Class III regulation.

The prior panel review concluded that Class III was necessary for BGS because they stated that it's "not known how a change to the device output due to device modifications may impact the clinical response to treatment." This remains true today. As I have discussed, waveform parameters are unique and proprietary to each device. The nature and extent of these changes is not predictable and some signal parameters have been shown to be ineffective to activate bone growth. And the performance of these devices remain today highly sensitive to device-specific manufacturing tolerances and preferences.

Per FDA, it's essential for FDA to assess any change that affects safety or effectiveness for devices with unique design characteristics or manufacturing processes. And as I've clearly shown you, these are unique device characteristics, manufacturing processes, and waveforms.

In 510(k)s the FDA requires only when a change would significantly affect the safety or effectiveness of the device. In contrast, under Class III, FDA requires PMA supplements for any change to a PMA-approved device that potentially affects safety and effectiveness.

Now remember, the difference between Class II and III controls is very significant. In up-regulating devices from 510(k)s to PMA, FDA noted that many design and manufacturing changes that led to device recalls were not required to be reported to FDA under 510(k). If these changes had been reported, the recalls could've been avoided. I want to remind the Panel that BGS has performed safely under Class III controls for 40 years and these controls remain important.

I want to also remind the Panel that BGS meets another criteria for Class III status.

They are of substantial importance in preventing impairment of human health. The Panel previously recognized this in 2006 and more recent data affirms it remains true today. The harms of ineffective BGS include severe adversities to patients' health and quality of life, as will be discussed next by Dr. Bhandari.

DR. BHANDARI: Thank you, Dr. Ryaby. I am going to share with you a few slides on evidence-based medicine and specifically, a call for continued high-quality clinical trials for the regulation of BGS devices and trauma applications.

Just as a matter of introduction, I am an orthopedic surgeon and a Professor of Orthopedic Surgery at McMaster University in Canada, holding a Canada research chair in evidence-based orthopedics. I've spent the better part of 20 years in the design and execution of surgical trials.

The FDA's position is consistent with EBM principles. We agree that preclinical studies are very important but are also hypothesis generating and do not confirm the effectiveness of a new BGS device. In fact, we need clinical studies. We need clinical studies, though, with bias-reducing measures to assure valid and scientific results. And quite frankly, the introduction of BGS without assurance of high-quality clinical trials really, quite frankly, risks harm to patients, and I'm going to speak to you a little bit about what we mean by that as we get deeper into this discussion.

But here's the point. In no other time in history have we really been concerned about a rush to under-tested treatments. And why? Because they place patients at risk. In fact, Gordon Guyatt, a cofounder of evidence-based medicine at McMaster University, stated the following: "You need to be skeptical about [COVID-19] treatments...if you really want to know, wait for the randomized trials." Level I evidence is critical, it's critical.

In fact, he wrote one of the most cited landmark papers along with Professor David Sackett defining EBM as the conscientious, explicit, and I'd say careful use of the current

best evidence in making decisions about the care of individual patients.

Now, in an effort to accelerate access to new BGS, we risk serious missteps and quite frankly, potential for harm. Buxton's Law says it's always too early until unfortunately, it's suddenly too late.

This is all too often occurring in the introduction of new devices and new technologies in orthopedics. In fact, one in four devices are pulled from the market within 5 years.

We can hypothesize that some of that, in fact, maybe a majority --

(Audio feedback.)

DR. BHANDARI: We conceal randomization, we blind and find independents of outcomes and assessment of outcomes. We also look at patient-important outcomes. We follow all our patients and ultimately, we assure our studies are large enough to be valid. We talk about appropriate sample size for appropriate study power.

But the clinical message here is randomization is a major bias-reducing measure. In fact, Level I and Level II studies really sit atop that hierarchy. In fact, when we look at what the FDA's consistency is with this, well, they're actually quite supportive of this notion, right, we need high-quality controlled trials. In fact, they say that a device is effective based upon well-controlled investigations. Once again, that will put us in Level I and Level II for the most part. These are prospective designs.

Now, what about the preclinical experimental data that we often spend a lot of time focusing on? Preclinical studies, as I mentioned, are critical in bridging the gap from bench to clinical subjects or patients, but preclinical studies do not replace a well-designed clinical trial. There's at least three important reasons. One, there are well-known differences between animals and humans with respect to bone-based cells. Two, fracture healing and spine models, particularly spine fusion models, are just inadequate. And finally, and

probably to me the most important, animal models do not adequately assess patient-important outcomes; the fundamentals of evidence-based practice, patient-important outcomes. Function, pain, and health-related quality of life are not appropriately measured and testable in animal studies.

Let's take an example. This is a trial that I was involved in and one that we led, called the FLOW Trial, a trial of many thousands of patients, about 2300 patients to be exact, published in the *New England Journal* some years ago.

The fundamental answer to this question was in very complex fractures, open fractures, did adding a soap solution improve outcome? In fact, we found quite the opposite, that soap solution was quite harmful and increased risk of reoperation. Now, keep in mind, this is a multinational, multicenter study well powered with thousands of patients. If we had focused only on our preclinical data, we would've been grossly misled. In fact, our preclinical data, in many studies, reported soap irrigation as the least toxic to osteoblasts and quite frankly, the best option to patients.

So had we listened to our preclinical data, we would've had a false positive finding and quite frankly, potentially harming patients with an ineffective treatment. There is risk to false positives and there's harm associated with false positives. We call this Type 1 or Alpha error. Falsely concluding the benefit of a bone growth stimulation device is problematic and, in fact, the risks are increased when we fail to use standard methodological safeguards. Safeguards you've already heard Dr. Ryaby speak about. Safeguards that include no controls, I mean, in this case, failure to have controls, failure to randomize, and failure to consider prospective designs. Preclinical designs are inadequate to assure -- or to assure limiting this Type 1 error.

And why do we worry? Well, let's look at this nonunion, for example. The impact of fracture nonunion on physical health is comparable to end stage of arthritis or in fact,

worse than a state of congestive heart failure. So it goes without reason that the profound effects on the quality of life experienced by individuals with nonunion, in this case you can see here, a tibial nonunion, can't risk having ineffective treatments. So even minute changes in waveforms, for example, can lead to clinically different outcomes and we cannot risk that without well-designed testing of prospective Level I and Level II studies.

This goes further. When we look at even spine, we also know that the consequences for ineffective treatments in spine is as difficult and as troublesome as it would be in nonunions. Remember, patients with spine problems, in fact, have pain, chronic pain, have poor quality of life and poor physical function.

I'm going to leave Dr. Lim to explain to you some of the consequences and some of the strategies for managing spine.

Dr. Lim.

DR. LIM: Thank you, Dr. Bhandari. I'd like to thank FDA for the opportunity to speak on behalf of my patients regarding the bone growth stimulator. I'm an orthopedic, practicing orthopedic spine surgeon in South Carolina specializing in deformity, degenerative processes, as well as fracture healing and treatment.

As you know, currently BGS devices hold a Class III classification with FDA and I believe it is necessary and required to continue to keep those classifications for the bone growth stimulator to ensure safety and wellbeing of my patients. And ineffective devices have poor clinical outcomes and unsafe devices have potential for injury.

As you are aware, bone growth stimulator patients have risk factors for failed spine fusion or pseudarthrosis. And BGS devices are essential for improved fusion rates following surgery and these patients who do not heal lead to pseudarthrosis. And current research shows that more of these failed back surgeries are more attributable to pseudarthrosis and currently, up to 50% of fusions lead to pseudarthrosis, and patients who experience

postoperative infections, up to 80% of those patients lead to pseudarthrosis. Inability to heal or ineffective fusions lead to pain and morbidity, too, with these patient and therefore adds healthcare costs as well as -- due to the reoperation cost as well as continued pain management, which some of these patients may require narcotics for the rest of their lives.

Not everyone receives a bone growth stimulator. Patients with comorbidities dictate whether they receive a device. These patients include smokers, patients with osteoporosis and osteopenia, diabetics, and vascular disease. And these bone growth stimulator devices act as an adjunct to fusion and they help treat, help in the treatment of failed spine fusions as well as fractures that are either fresh, delayed or nonunions.

Spine is unique in the sense that surgical approach, anatomy, and injury affect the healing. A two-level fusion from anterior is not the same as two-level fusion from posterior in regards to its healing, and bone graft also makes a vast difference in how the fusion heals. The gold standard is an autograft bone graft; however, these patients with high-risk factors have poor quality bone, which will lead to increase of arthrosis, therefore necessitate a bone growth device to help the fusion.

As you can see on the right here, this is a perfect example of a pseudarthrosis. The fusion has not healed, causing cutout, and this is around the screws. This is a perfect setup for catastrophic failure with possibly even paralysis from complete failure.

At this time I'd like to give you a clinical example of a patient who I truly believe would benefit from a bone growth stimulator. This is a 68-year old female with a prior multilevel fusion at an outside institution who presents to me with pseudarthrosis with kyphotic deformity and hardware failure. And of course, she presents with comorbidities including diabetes, obesity, and osteopenia.

As you can see on the preoperative CT scan on the left here, she has failed to heal the interbody fusion at L5/S1 with collapse of the disc space leading to screw lucency at S1

and hardware failure. And you see on the right, this is the patient doing her best to stand straight; however, she has a kyphotic deformity. Based on presentation, patient had severe pain with severe loss of quality of life, and she pretty much spent all of her days in a wheelchair unable to ambulate. This patient required a large reoperation with removal of hardware and extension of fusion down into the pelvis with redo fusion at the level of L5/S1. I do believe that this patient, with an effective bone growth stimulator, would've benefitted from the device and would have had a better chance of healing that fusion the first time around without the increase in morbidity to herself, as well as decrease in quality of life and the burden to healthcare.

NASS is an independent professional society comprised of neurosurgeons and orthopedic spine surgeons, and in August 2016 they put out a policy recommendation recommending BGS devices for fusions of two or more levels, revision fusions, and smokers and any patients with diabetes, inflammatory arthritis, vascular disease, and osteoporosis.

And this independent panel created at NASS looked at all the quality data, including a wide range of data, including high-quality clinical data as well as bench work and basic science, and they came up with the policy recommendations for bone growth stimulators recommended for fusions.

And going forward, high-quality clinical trials are essential and not all bone growth stimulators are equal. We require structured, high-quality clinical trials and PMAs that are necessary to ensure effectiveness and safety. And high-risk patients continue to push boundaries of fusion healing and these BGS devices mitigate increased rates of pseudarthrosis.

Our patients are getting larger and older at this time and deregulation and elimination of PMA will lead to ineffective devices. Ineffective device is essentially treating the patient with a placebo which will create harm and therefore increase burden to

healthcare costs with continued pain management and reoperation.

In summary, bone growth stimulators for high-risk patients are vital for high success of spine fusions. An ineffective device leads to catastrophic failures with reoperations, which are highly morbid, and continued pain with lifetime pain management and narcotic use. And these lead to increased burden on healthcare as well as society, in general. And an ineffective and placebo device may lead to patient injury, as well. And as clinicians, we need high-quality data to support our clinical decisions, and these high-quality data will demonstrate safety and effectiveness with bone growth stimulators going forward.

And at this time Dr. Ryaby will give a few closing remarks to our presentation. Thank you.

DR. RYABY: Thank you, Dr. Lim. In summary, Class III status for BGS is consistent with FDA's mission to protect and promote patient health. In 2007, FDA concurred with panel findings that there were fundamental knowledge gaps that precluded reclassification. We believe that these gaps persist today. Level I or II clinical studies are still necessary to demonstrate efficacy of new BGS. Class III best ensures this level of evidence.

As I clearly showed you, BGS are not a generic type of device. Instead, these approved devices represent wide-ranging, varied technologies that are not completely understood. For 40 years, the totality of Class III controls has ensured that approved BGS are safe and effective.

There is no evidence today to show that BGS and safety and effectiveness can be assured without these Class III controls. In fact, information that was presented today shows that without Class III controls there can be ineffective devices. The risk of these inconsistent or ineffective clinical treatments would present unacceptable risks to large and vulnerable patient populations. There continues to be no substitute for substantiation of BGS safety and effectiveness except by rigorous clinical data and FDA pre- and postmarket

review of BGS manufacturing and all modifications. In other words, Class III controls. Reasonable assurance of safety and effectiveness for BGS is provided only in Class III.

Thank you and we'll now take questions.

DR. SMITH: I want to thank all the Open Public Hearing speakers for addressing the Panel today.

One point of clarification before we do question and answer, I'd like to remind the Panel that the FDA has asked us to evaluate the bone growth stimulators under the indications for established nonunion secondary to trauma as an adjunctive device. With that said, I would now like to ask if anyone on the Panel has any questions for our speakers.

DR. PFEFFER: Glenn Pfeffer. My video doesn't work again. Should I ask my question?

DR. SMITH: Yes, sir, we can hear you.

DR. PFEFFER: Okay, good. I'm probably not worth looking at, anyway. Okay. So I have a question. Thank you, these are all excellent talks. Okay, now I can start it. And I appreciate the work you've put in.

The question I and I'm sure all of the Panel has is we appreciate the diversity of bone growth stimulators, they're certainly not generic, but neither are total joints. There have been many total joints that have come onto the market lately, particularly total ankles that are Class III -- sorry, excuse me, Class II classification.

And certainly, a surgery with an implanted joint is -- has more potential risk than a bone growth stimulator. I use bone growth stimulators, I'm an orthopedic surgeon at Cedars-Sinai, but how could we argue to classify bone growth stimulators as Class III if total joints are only classified as Class II, as are many other equivalent devices by the FDA? If we look at FDA precedent. You'd have to be asking FDA and us to change FDA precedent and if that's what you're asking, I think that's a superb question. But without changing FDA

precedent, I don't know how we could possibly think of these as anything but Class II. Thank you.

DR. RYABY: Dr. Smith, I'll start the answer to that. Well, what we're really asking in this meeting is to reclassify from Class III to Class II and I think we've given you the examples of why these devices should remain in Class III. Number one, any new device or, in fact, new application of these devices should be based on Level I and II clinical evidence. And secondly, the issues of manufacturing these devices require FDA review of all premarketing proposals as well as inspections of the preapproval device.

And so we don't think these are akin or comparable to a metallic internal fixation total joint replacement. In fact, as I spoke, the nuances of the technologies are such that only the manufacturers really have that knowledge and, as Dr. Bhandari said, without this prospective randomized blinded clinical evaluation, the risk of having an ineffective technology would put large patient populations at risk. We didn't really talk about appendicular indications, but think about screw nonunion applications for fractures that aren't healing, as well as all of the issues around, as Dr. Lim said, spine patients. And I'd like to ask Dr. Bhandari maybe to answer a little bit more on the clinical side.

DR. BHANDARI: Sure. I think the point I raise is that when you look at any implant --

DR. RYABY: You're unmuted, Moe, I think.

DR. BHANDARI: Can you hear me? Can you hear me?

DR. SMITH: Yeah, we can hear you.

DR. BHANDARI: Okay, great. You know, I think the challenge to Dr. Pfeffer's point, too, is even beyond total joints. Let's look at intramedullary nails, for example. These are implantable devices that have a relatively reproducible -- relatively reproducible action. You can argue, I guess, in that case, yes, they are invasive but they do differ, in my mind, to a bone growth stimulator which in many ways as you look at the reality of what's happening

in terms of the way, you know, the preclinical data that supports its biological actions, it does seem to me to be somewhat different. Even though it's an external device, it just seems to be different because -- well, I mean, I'll use that as my standard, I guess, response to Dr. Pfeffer's point. I do think of them somewhat differently. Although it's still noninvasive, it has a biological action which might be perceived differently than a total hip replacement or another implantable, let's say, intramedullary nail or plate device.

DR. SMITH: Yes, Dr. Lim.

DR. LIM: To Dr. Pfeffer's point, you know, with a -- I'm an orthopedic surgeon, as well, but for a total joints device, it's asking us to essentially be compared to a bone growth stimulator device, asking us to implant the device and doing the mechanical testing while it's inside the patient. You know, with the bone growth stimulator, we're unable to do an effective study or safety study until the surgery's finished and we study it, how we use it on the patient themselves. Whereas any implantable device like a total joint or pedicle screws, you can do mechanical studies to make sure they could withstand the mechanical forces before they're implanted into the body. So I think there's a difference.

DR. SMITH: Yes, Dr. Finnegan.

DR. FINNEGAN: So I have to ask at least one rude question per panel. Can the BSG (sic) tell us why there has been absolutely no improvement in information for 13 or 14 years?

(Pause.)

DR. RYABY: My status had changed and now I'm back live. So, Dr. Finnegan, I don't agree that there's no new information. In fact, there certainly have been a lot of new peer-reviewed publications, including data from randomized clinical trials that continue to show the applicability of these different technologies, and this is since the last panel meeting. In fact, there are two meta-analyses done in the past year, one published by Johns Hopkins

neurosurgery, another one led by Dr. Aleem at the University of Michigan and Dr. Bhandari, who have actually shown, in a very rigorous statistical way, the benefits of these devices. So I think where you're correct is that there have been no new indications, but as I alluded to in my slides, there are several IDE clinical trials under way, for example, using a pulsed electromagnetic field as an adjunct to rotator cuff injuries that need to be surgically repaired, that's a 540-patient double-blind, randomized, multicenter prospective clinical trial. So there are efforts under way to expand the usefulness of these devices in orthopedics and neurosurgery, but again, we're going to have to wait for that Level I clinical data to be available.

DR. SMITH: I have a question I'd like to ask the Panel. If a manufacturer or someone were to generate a device that had whatever proprietary waveform and coil design so that on a spectrum analyzer in a tissue phantom the delivered EMF field would be within the parameters of the existing devices, would that be sufficient for a 510(k) application?

DR. FINNEGAN: Aren't the technologies proprietary for each company and each piece of equipment?

DR. SMITH: Exactly. Actually, my question will be if electromagnetic field, coil design, pulse function, if someone in a different manner, and I don't do these things, but if someone were able to design a device and however they did it, had whatever wave function and coil design, just as Dr. Lim was alluding to, we put the joints, we can put these things on all kinds of analyzers to assess the wear characteristics and biomechanics. However they do it, if there's a device that delivers the same EMF fields which are in within the treatment parameters established in the literature, would that be sufficient for a 510(k) application?

DR. MUIR: Is that a question for FDA?

DR. SMITH: No, for the Panel. I'm just trying to just get a sense of where we are in the discussion.

Yes, Dr. Gilbert.

DR. GILBERT: Along those lines, the question I came at was similar to what you're saying but may be more from a scientific side, you know, what is the science that defines what is effective and what is ineffective in terms of waveforms? We've heard a lot of discussion about waveforms are generated with this technology and that technology, and there needs to be some constrained, defined parameters for that technology, but I haven't heard anybody tell me what that is, how narrowly defined is that, how do you know that your waveform and your design is optimized for the clinical treatment? Just I need more information from the speakers about what's that science, what do we know about what's valid and not valid in terms of treatment and how do we know those things.

DR. SMITH: Thank you, Dr. Gilbert.

And I think we have about 3 or 4 minutes left before we start the Panel deliberations, so I'd just like to focus that this is our opportunity to discuss with the presenters and then -- before we move on to the Panel deliberations, so if there's any remaining comments or questions for the presenters, this would be the time and then we'll move on to the Panel deliberations, which will be a discussion amongst the panelists.

Dr. Ebramzadeh has a question.

DR. EBRAMZADEH: Yes, I'd like to comment on one aspect that was spoken about, the hazard of making a Type 1 error in clinical trials or experimental design. We've all been indoctrinated to think that that is the original sin, to make a Type 1 error, that is decide or conclude from a study that there's a difference when in reality there is not and we rely on the p-value and we compare it to Alpha which is always 0.05 and we decide whether the study was good or not.

But to be objective, we have to also consider Type 2 error which, in this case, would translate into "a device works" and we falsely conclude that it doesn't work because our

study was -- didn't have enough power or had confounding variables, etc. And so a good study doesn't just minimize the Type 1 error, that is a fallacy. It optimizes Type 1 and Type 2 errors and unfortunately, many clinical studies are designed only with Type 1 error in mind. So this would affect the decision-making process here where a lot of technologies would not be really given a chance because they would have to prove themselves, but it involves -- the optimization of Type 1 and Type 2 errors involves risk-benefit assessment of the particular clinical issue at hand.

We can't compare this to COVID-19 issues, whatever they may be. I guarantee you, a vaccine is going to come in to play before really large-scale great clinical trials are done because we have to make decisions based on partial data, and that's the probability game that we have to do in clinical trials whether we like it or not.

DR. RYABY: Dr. Bhandari, do you want to comment on Type 1 and Type 2?

DR. BHANDARI: No. I mean, I fully agree. I mean, our group particularly believes that you have to balance the two. Type 2 error is prevalent. I'd say 80% of studies published in orthopedics if not more that are negative may, in fact, be suffering from the Type 2 error, so it's rampant in our field.

The big challenge, I believe, for the FDA though is to have that balance in mind and look at what's greater harm from the point of view of patients to take a potentially effective treatment that for whatever reason the company didn't do a big enough study and never got out to patients, yeah, certainly we are preventing them from having access to something that may work. I would personally agree the more egregious risk is putting something on the market that's commercial that has no benefit yet it's purported to have benefit. So that's -- I mean, for me personally, focusing on Type 2 -- focusing on Type 1 false positive has a greater potential risk, not to minimize at all Type 2 being a problem.

DR. FINNEGAN: You're muted.

DR. SMITH: Excuse me. Before we move on to the Panel deliberations, we're about a minute over time, but if anyone right now has a question for any of the presenters, this would be the time. And then we'll move on to the Panel deliberations and at that time if a question should come up for the presenters, they can be addressed then, as well, but I would like to ask respectfully that we, within the next minute or so, move on to the Panel deliberations.

But Dr. Price raised her hand and Mr. O'Brien raised his hand as well, so if you two have any questions for the presenters, please address them.

DR. PRICE: Yeah, I'm seeing a lot of methods, but -- and that's interesting, that's all and good, but Dr. Smith asked the question about if we have equivalency in terms of waveform or some other technology and there has been a pattern of working, I'd like to ask the speakers is that like, is that sufficient?

DR. RYABY: Yeah, I'll answer that. As I said, there are proprietary aspects to making these signals and the way you measure them, the way you set your specifications, Dr. Smith even mentioned coil design or transducer design. So it's not a matter of just the output power of, for example, ultrasound or the electromagnetic field, it's actually all of the fundamental engineering that makes these devices unique.

DR. FINNEGAN: So would it call for transparency if you want to have this -- the device approved or would that be useful?

DR. RYABY: Well, you know, having worked on the corporate side for most of my career, obviously these proprietary features of signals are things that the four companies in this case are very devoted to maintaining the proprietary nature of these signals. So I think the fear of a new electromagnetic field or ultrasound signal not being clinically tested at a high enough level of rigor to really ascertain how safe and effective this is, that's what Class III brings to these technologies and other technologies, and that's what we're afraid of if

these devices do get re-classed to Class II, is that the special controls will not guarantee the level of clinical evidence to support their true safety and effectiveness.

DR. FINNEGAN: Thank you.

DR. SMITH: Thank you, Dr. Ryaby.

We're 4 minutes over and at this point, in deference to the remainder of the schedule, we're going to proceed towards the Panel deliberations and thank you for this very informative discussion. At this point I will pronounce the Open Public Hearing to be officially closed and we will proceed with today's agenda.

It's now time to open the floor to the experts around the table to begin deliberating on the topic of noninvasive bone growth stimulators from what you heard during the Open Public Hearing, the FDA presentations or the material that you may have read in your panel packs.

Do any Panel members have a question or comment for the FDA or want to discuss a particular issue among the Panel? Panel, please remember to turn on your video monitor on your computer when you speak. You can raise your hand and I will call on you.

Yes, Dr. Pfeffer.

DR. PFEFFER: Thank you. I have a question for FDA because I, for one, am completely incapable of making a decision for this Panel because I don't have the right marching orders or the right rules. I don't know how fast or slow to go on this road, right? Can't get a ticket if there are no speeding limits.

So what I mean is, is this Panel, FDA, the start of a new era for you where new products will be tested under PMA at the most rigorous Level I evidence? I think it should, but I don't think that's what you want because you also have a mission of doing things as cost effectively as possible. So I, and I think all of us, need to know that because if this Panel deals with precedent, then the precedent clearly supports this being a Class II but

very controlled device. There is as much difference in total joints coming on the market as there is in variations of bone growth stimulators and no one can prove that otherwise, in my opinion. So I ask FDA the question, is this the beginning of a new era or are we working on precedent of what you have considered previously Class II devices?

DR. MUIR: So this is Jesse Muir, so I can speak on this a little bit. I would not describe anything that we're proposing today to be a change in era, but more of a continuation of how we've always reviewed devices and also looking at consideration of the benefit-risk approach that we look at devices historically. You know, this is nothing new in terms of the questions that we asked, how we look at it, how we regulate devices. The consideration of the Class III versus Class II is something we've always considered in looking at devices and we have down-classified and up-classified, based on historic evidence in the past.

So I wouldn't say anything has changed or anything is new with what we're looking at today, but what we are looking at is do we believe that we can establish special controls and to demonstrate that these devices are safe and effective. For the 510(k) pathway that would be through the substantial equivalence determination, not the unique safe and effective, but looking at this narrow group of devices, the external bone growth stimulators for adjunct fixation of a fracture, is there sufficient evidence that the special controls that we're proposing are sufficient in combination with using the clinical data as a special control?

DR. PFEFFER: Good. Well, thank you, that helps me. So then the same guides you've used to approve completely different total joint designs, I know about foot and ankle, is the same thought process I should use here for deciding whether this is Class II or Class III, that's basically what you're telling me. Since I'm aware of what FDA has done with total joints because I was on an FDA panel dealing with that.

DR. MUIR: Yeah.

DR. PFEFFER: That's very helpful, then. Thank you very much.

DR. SMITH: Yes, Dr. Ebramzadeh.

DR. EBRAMZADEH: I have a question with regard to the technologies, the trade secrets, as they call them, waveforms, etc. Are these patented and protected by patent or are they just trade secrets in the sense that nobody else can figure them out and they're just not checked?

DR. MUIR: Well, obviously I don't know the full status of the patent control for each device, and everything that is submitted to us is protected through confidentiality, so we're not allowed to obviously speak on the nature of any of the signals, whether they're under patent or not, I am not currently aware. Some of these devices have been on the market for -- as noted, over 4 years.

DR. SMITH: Yes, Mr. O'Brien.

MR. O'BRIEN: Yeah, this is a question for Dr. Muir, I guess. I was going to ask this of Dr. Lim for qualification, but since you did your literature review, I guess it would be appropriate to ask of you.

What's unclear to me, I mean, I can certainly personally attest to myself and tens of thousands of patients the importance of pseudarthrosis and concern because it does, in fact, create harm and not within the 9-month period, it seems to be a much longer time period. It still seems to be attributed to a significant amount of the revision surgery that's required and revision surgery has both personal and societal burdens all the way across the line.

What I'm not sure about is when you see the revision surgery, for example, the complication rates, let's say revision surgeries and it was quoted by Dr. Lim, I believe, that upwards of 50% of those revisions are, in fact, pseudarthrosis which doesn't occur within 9

months, but that's beside the point. The question was with the studies, when going through the literature review, what I'm not clear on is how many of those patients, in fact, revision surgery patients with pseudarthrosis did or did not wear a bone growth stimulator.

DR. MUIR: So for the literature search that we did, what we -- how we narrowed it down was looking at only published literature of clinical studies using FDA-cleared devices for on-label use. Off-label use has been discussed earlier in terms of treating early on, but these are looking at treating to an existing nonunion, so looking at the proper labeled use of these devices.

Unfortunately, a lot of patient-level data is not available. Being literature from various studies, it's really unclear, the revision surgery rate in these studies, but what we did find was some assessment of device-related adverse events with very, very low reporting, at least one report of the roughly 10,000 patients. They identified clinical success as a union. We don't have evidence at a patient level of -- for these studies for the patients who did not get a union, was there revision surgery and what was the follow-up process, but we can assume there was some follow-up, likely assume there was some follow-up on those patients.

DR. SMITH: Ms. Bonnell, you raised your hand earlier.

MS. BONNELL: It was simply to clarify that there is a high likelihood that those manufacturers do have IP protection for their particular designs, to an earlier comment there.

DR. SMITH: Thank you.

Dr. Yang.

DR. YANG: This is a question for Dr. Muir and the FDA. Given that special controls or the ability to establish appropriate special controls would allow this to be re-classed into Class II, and also given historically that in 2006 there wasn't enough information to establish

the special controls, can you summarize for me what the FDA's strongest argument is that we have new information, that today we have enough information to establish special controls?

DR. MUIR: So what I can discuss is that we're looking at here what data is available and we're taking a look at do we believe that the data that we have on hand, so a combination of 40 years of clinical experience, MDR risk, the lack of recalls for the devices due to patient harm, demonstrating and supporting safety, as well as very extensive literature going back throughout the life of these devices, do we believe that the evidence we have supports the use of the proposed special controls.

DR. YANG: So the data that you're talking about, though, it would've been available in 2006. I think what I'm mostly interested in is what has changed or can you summarize, in your view, what has changed between 2006 and now, what's the new data? Because it seems like everybody keeps talking about all this data being very old, very old, very old, and Dr. Finnegan mentioned something about nothing happening in the last 13, 14 years, so that's what I'm trying to get, in my mind, trying to make this decision, what is new -- what is new in the last few years that tells me that okay, now we have enough to do special controls today they didn't do in 2006?

DR. MUIR: So we do have additional -- make sure I'm not muted, sorry -- have additional data that we looked at when we did this presentation. So one group of information that wasn't really available in the last Panel was the prior SSED data from utilizing the 6-year rule. So that was a fairly recent available dataset that was available while -- this data is internal, we were not able to use this in our recommendation for the establishment of special controls in the prior Panel.

In addition, we have an additional 14 years of use data, MDR analysis, and follow-up studies for the devices that have been marketed including devices that had just come on

the market at that time. The CMF device, I believe, the CervicalStim device had just been marketed right around the Panel and was not part of that discussion. We now have the SSED and postmarket data on that, as well.

DR. YANG: So given that to be the case, it seems like safety is less of an issue than effectiveness in the CervicalStim data, by your own admission, didn't show any significant difference at a year out and we're talking about more than a year out. So the effectiveness part of this is still a big question in my mind.

But assuming that what you say can be taken at face value, then I have a follow-up question which basically is, given the heterogeneity of the energy source, given the heterogeneity in primary versus adjunctive therapy, appendicular versus axial therapy, the special controls, would you not think that they would have to be a huge list of special controls and do you think it's adequately able to address the concerns in this case for such a wide variety of devices?

DR. MUIR: No, I think that's a great question. And so when we looked at these devices, generally, our view of these devices is that we can bucket the risks into certain risk categories that are mitigated generally with the same special controls, so we are concerned of electrical safety of the devices, any biologic reaction to the devices, and in the end of the day, I think the main discussion we're kind of walking around is are they effective, is the effectiveness of the device, and the only way we see that being demonstrated and I think we concur with the industry presentation is that clinical data, valid scientific evidence of clinical efficacy is needed as a special control.

DR. YANG: Thank you.

DR. SMITH: We have -- thank you. We have four people that raised their hands. I'm going to call them out in order. It will be Mr. O'Brien and Dr. Gilbert and Dr. Alander and then Dr. Ebramzadeh.

Mr. O'Brien.

MR. O'BRIEN: Yes. Just to go back to you, Dr. Muir, if I could, flip it around in a different way. In a little bit we're going to be asked a question about substantial importance of preventing impairment of human health and it states that the FDA assesses that this is not substantial, BGS is not substantial, and I wanted to ask you why, in your mind, as it relates particularly to pseudarthrosis.

(Pause.)

MR. O'BRIEN: Dr. Muir?

DR. MUIR: I'm sorry, could you restate the question? I missed the first few words of that.

MR. O'BRIEN: Okay, yes.

DR. MUIR: I apologize.

MR. O'BRIEN: Pretty soon we're going to read a question that says if the FDA has assessed that there is no substantial importance of preventing impairment of human health with bone growth stimulators. My question to you is particularly as it relates to pseudarthrosis, how do you come to that assessment?

DR. MUIR: So when we're looking at the assessment of the risks to health, we're primarily looking at risks of harm, two subjects, so looking at the MDR risks for burns, side effect, any other adverse events related to the device. At the same time, the efficacy studies would address the risk of lack of device efficacy which would lead to pseudarthrosis or nonunion, so from the aspect of the concern of the patient harm due to the device not being effective, which is likely resulting in the pseudarthrosis, that is where we're looking at special controls as a method of mitigating that risk.

MR. O'BRIEN: Well, as you said with that, if I might, in your presentation and we also heard from Dr. Lim, etc., that the symptom related to pseudarthrosis is pain and pain was

actually number two on your adverse events.

DR. MUIR: Yeah, pain is a very common adverse event and unfortunately, we don't have the -- I think this also came up in the first Panel, the nuance data of MDRs to trace in each patient where pain was recorded, you know, how -- what was that related to, was that related to pain just at the fracture site due to healing, pain due to pseudarthrosis, pain due to just the patient having pain due to having a recent fracture. I think the one thing to note, though, was the total count from that pain was roughly 200 reports and this is over -- 1984 to last October was the MDR search, so even though it was the most common adverse event, the overall rate of the event is extremely low.

MR. O'BRIEN: Yeah, it's underreported. Thank you.

DR. SMITH: Thank you.

Dr. Gilbert.

DR. GILBERT: Hi, it's Jeremy Gilbert. So I was just thinking this through a little bit. The safety elements of this, I agree with Dr. Muir that we have a lot of time to assess the use of this, over which to assess the use of this device and that additional 15 years or 14 years, I think, has added to that safety part. So I'm less concerned about the safety.

The main thing I heard was the failure of the treatment to deliver a healing effect, right, to overcome the pseudarthrosis, so the nonunion and that's clearly an efficacy discussion that boils down to the waveform, the energy delivery, things of those sorts that go to the clinical efficacy of this and I don't see -- the harm of the device, I could break it down into two things, the harm is what if that treatment causes something you don't expect, it heats you up, it causes some other biological reaction that you don't anticipate, that's one harm of the device.

The other side of the harm, it seems to me, was the harm of it not actually working because it doesn't have a waveform that fits the magic propriety waveforms, that those

who have gotten PMA have figured out. But they don't know what all the other possible waveforms are that could deliver an as effective or perhaps more effective treatment with this sort of an approach. And I do agree that the design of a clinical trial to assess the efficacy as a special control would address that and I don't see additional harms of the device itself raising enough of a concern to say it needs to stay in Class III. So that's my comment.

DR. SMITH: Captain Peat, did you raise your hand?

DR. PEAT: Yes. A very good question. I was just thinking a little bit more about what you said and not just related to when we're thinking about skin irritation and wavelength and so forth, not just a matter of us actually keeping in special controls that have clinical data, but we also are looking at biocompatibility, we're looking at other nonclinical studies that can also support some of the concerns that we raised earlier.

In addition to that, I just wanted to bring forth some communication just to narrow the scope of some of our discussions that we're having, and one of the things that we thought about when we were coming to reclassify these particular products is the fact that we have robust data and it's to the point of when we look from what we saw in 2006 and now we're here, we are in 2020, we have narrowed the scope and the discussions in 2006, it was talking about all BGS.

And so today we're bringing in noninvasive bone growth stimulators for established nonunion acquired secondary to trauma or as well as using it as an adjunct and to point to the postmarket data.

So this product has been in existence for 4 decades. Over the 4 decades we have only had close to 300 MDRs that have come about and within the 300 MDRs, we've had about 200 of those speak to skin irritation, which we've put into for a nonclinical test and as well as clinical testing, and only about a small fraction of that, which was about 16 reports,

goes to pain. When we looked at the body of literature, there are over 11,000 patients that we have looked at to really come up with our analysis as to what the adverse events are and the recalls are very low. I know there's more and we were discussing a lot about more primary treatment and I just want to make sure that you all understand that when we brought this to you all here in 2020, we wanted to really focus on this narrow scope with the body of literature that is there and noting that we are just proposing Class II with special controls, but also in addition to that we are indicating within that special controls that we still have clinical data.

So when you go into your deliberation with the questions that we have posed, I would really like to hear your thought process based on the information as proposed within our Executive Summary and the discussions that we've had here today and note that it's not all of BGS, which our previous presenters spoke about, but we're really narrowing the scope to this small aspect of BGS.

DR. SMITH: There were two other Panel members that had pending questions.

Dr. Alander.

DR. ALANDER: Dirk Alander. I have, I guess, a question and then a comment. The first would be that, Mr. Muir -- Dr. Muir, I didn't quite get that 6-year rule that you referred to in '06. I'd like to just clarify that.

DR. MUIR: In the mid-nineties there was -- I forgot the exact year, but in the mid-1990s FDA established what we kind of colloquially refer to as a 6-year rule, which allows the Agency to utilize data from a PMA that has been on the market for more than 6 years. However, when it was established, PMAs that were approved prior to the generation of that rule were excluded from use at the 6-year rule. So earlier in the first half of the presentation I mentioned some studies being too old. In that case I was referencing the studies that were clinical studies performed before the existence of the 6-year rule.

DR. ALANDER: Okay, thank you. The comment, I guess I would echo Jeremy's thoughts. I think if we could define that healing factor, whatever wavelength it is, whatever method it is, and be able to measure, that would go a long way. But I think as far as the safety issues, I think I'd echo Jeremy's comments.

DR. SMITH: Thank you.

Dr. Ebramzadeh.

DR. EBRAMZADEH: Yes. Also following up on what Jeremy said, he almost had the exact same thought that I had, which is by trying very hard to be sure that a device is not introduced that doesn't function as well or doesn't function at all, we are also decreasing the probability to develop a device that may work a lot better, we don't know, especially since so little is known about the way these waveforms really biologically do their interactions and so forth, we have to consider that as a factor in our decision. I think it's a major point.

DR. SMITH: Thank you.

Dr. Osborn.

DR. OSBORN: Thank you. Just so I'm clear in my own head, if we do reclassify as proposed, do -- will we see this surge of generic, for lack of a better term, BGS products that enter the market or the special controls, do they control that introduction into the market with good evidence before they can be marketed effectively?

And to me it's just -- it's very similar to having two athyroid people in my household, the constant battle that still is ongoing with the FDA in synthroid versus generics is very near and dear and I think the ability to not look at something that's an implant and something that you have to trust essentially as a medication that is going to be just as efficacious, there are some concerns and insurers and others wanting to go with the lowest priced but unproven product. So I guess I just need clarification on what the reclassification

actually does to the marketplace with uncontrolled or unproven products.

DR. MUIR: That is a very difficult question to answer in that, you know, we don't control the market. What comes in and what we review is going to depend on industry. I can't speak for what industry will submit or plans to submit to the future. That said, you know, we will be -- should this be down-classified to Class II with the proposed special controls, we will be using this to make sure that we are using the same standard of valid scientific evidence to support the use of these devices.

DR. SMITH: And I'd like to enter a comment to the FDA or Dr. Muir, specifically, just to help educate me and then also may ask a question. If these are classified as Class II, is it possible to then, as part of the restrictions or expectations, to ask for demonstration of certain performance parameters? In other words, as the presenters from the public hearing have shown, they've done tremendous work and it's been 40 years of evidence of particular things that do work, but I would have some reservations that someone just makes a coil and says trust us, it will work without knowing anything about it in that EMF field, is there any way to ensure that however they do it the mechanism delivered is within certain parameters? Or would we be saying that anybody who produces a device that generates a pulsed field that's in a predicate device?

DR. MUIR: Oh, absolutely. And it's been touched on both by the industry and some of the Panel members that, you know, each of these devices is unique, it's a very different signal for each device and even two devices using the same technology may be using very different signals. One pulsed electromagnetic field may not be the same signal as a different pulsed electromagnetic field.

As part of the special controls, we did include a recommendation of a control to include a characterization of the signal being provided such that we can establish some understanding of what the signal is, as well as we would be -- in terms of addressing the

other special controls for electrical safety and adverse biologic reaction, we'd be looking at testing for signal energy, signal pulse width, you know, in addition to full characterization of the signal, a full evaluation that this signal is not generating any energies outside of safe fields. We don't want a device on the market that is generating unsafe signals either biologically or especially in terms of electromagnetic compatibility with other potential implants or medical devices. This is something that we would look at for any device regardless of 510(k) or PMA and we've made -- we wanted to make sure that that was included in the special controls.

But I think, also, touching on an earlier topic, it is a potential that a company could come in with a different signal, say a new PEMF device that had its own unique signal and just like if they came in as a new PMA, we would be looking at what clinical evidence do they have to demonstrate this new signal generates an effective as well safe treatment.

DR. SMITH: Ms. Bonnell, you had raised your hand earlier, do you have a comment?

MS. BONNELL: Sure. This is Stacey Bonnell, non-voting Industry Rep, and this is back to a comment regarding impacts to industry. I can make a few comments there that might be insightful.

So representing Johnson & Johnson/DePuy Synthes, I can disclose that we do not have similar-like products that are commercialized. It is possible that my company and competitor companies may have at some point considered commercializing bone growth stimulators that are being discussed here as a result of the Panel's recommendation here and the subsequent FDA actions.

In addition to my role with J&J/DePuy Synthes, I also serve in a leadership capacity for an industry advocacy group, OSMA, Orthopaedic Surgical Manufacturers Association. We're right now with 35 member companies and we did poll our membership and we recognize that there is not a unanimous position regarding appropriate classification of

noninvasive bone growth stimulators. It is likely that the divisiveness is because there are commercialized products and invested companies compared to those who don't have that access to the market.

OSMA's mission is for -- we advocate for, and work collaboratively with, standards development groups as well as FDA and then professional societies for the appropriate regulation and guidance formulations and also to prioritize -- recognizing that FDA is embracing least burdensome provisions, that being the lowest classification possible, keeping in mind both serving in the capacity of the U.S. public safety as well as their resources and capacity of the FDA staff, as well.

With the change, if there should be a change in the classification as a result of this particular Panel, it would open up opportunities for additional advancements in the technological field, I think you heard that earlier in the open public comment, that the higher classification could be serving as a potential limiting factor for innovation and development of the technologies here.

But I want to go back and emphasize again that there is the potential for the development of standards for the different stimulation types, dosimetries, frequencies, almost all of those technological parameters. I would emphasize that those are needed special controls within the performance aspects of the device.

DR. SMITH: Dr. Price.

DR. PRICE: Yeah, I just need to ask everyone here what -- what I'm struggling with is I see the innovation being prodded out, that makes perfect sense. I see a basically harmless protocol in terms of like safety, like fused skin blisters or whatever. There's going to be postmarket surveillance of the new products, clinical data is going to be asked for. So I'm really not sure where all the excitement's coming from. In terms of this is not a COVID-19 like vaccine, it seems to be something that people have been using for years and years and

it seems to be relatively safe. If it doesn't have efficacy, it's also not likely to stay on the market because people are not going to continuously use what doesn't work, and I think that the efficacy thing is like a problem across all medicine and devices, I mean, over and over again we see devices that have gone through trials and have done all these things and were apparently God's gift to medicine and it turns out, you know, like for arrhythmias and things like that or tPA, we're seeing that wasn't the be-all/end-all to have a clinical trial. So what is the most practical, in terms of like -- and I'm asking you, I don't know, I'm asking you what is the most practical choice that we can make for best safety, which there's not much of a safety issue. And for efficacy, are there things that people would maybe need to declare?

I like the idea of Dr. Smith's where a certain -- there would be certain standards for certain forms and if they met that standard then, you know, that helped. But I'm sure that's already embedded. So those are -- that's what I'm asking, I'm -- my concern is I studied at Oxford with evidence-based medicine and I appreciate evidence-based medicine and I would say that it changed my life, but there's also a certain -- there's also a certain authority driven "this is the way it must be because of error one and error two and all kinds of like this" and I'm not -- and I think our responsibility here is to make the best decision, the best decision for the people. So that's my -- I'm laying that out there. Sorry I talked so long, I just didn't know how to express it shorter.

DR. SMITH: Are there any other comments before we move forward to the questions?

(No response.)

DR. SMITH: Before we move forward to the questions, I would like to ask the FDA for a point of clarification, that as we address these questions, it's my understanding that with respect to these products we are looking at the indications for an established

nonunion in the setting of trauma as in an adjunct device, and I'd like to clarify that that is correct and that is how we should be framing our thoughts as we address these questions moving forward.

DR. MUIR: Yes, that is correct.

DR. PEAT: This is Captain Peat. That is correct, that is exactly how we would like you to frame those particular questions, yes, for those indications for use.

DR. SMITH: I saw a few hands go up, I don't want to move forward if anyone had any questions.

Mr. O'Brien, you raised your hand and then, Dr. Price, you raised your hand, as well.

MR. O'BRIEN: I thought I understood, but now I'm just confused. This is trauma or as an adjunct, right, not trauma as an adjunct.

DR. MUIR: So I can speak to this. This is Jesse Muir.

MR. O'BRIEN: In the case of spinal fusion.

DR. MUIR: So this could be -- these are all -- all the bone growth stimulator devices that we are currently looking at are approved for use as an adjunct to primary fusion. This could be -- fusion could be due to spinal fusion or following trauma for the long bones.

DR. SMITH: Dr. Price, did you have a comment?

DR. PRICE: No, I was just waving uncontrollably, sorry.

DR. SMITH: At this time let us focus our discussion on the FDA questions. Copies of the questions are in your electronic documents and can be found on the FDA website. I want to remind the Panel that this is a deliberation period among the Panel members only. Our task at hand is to answer the FDA questions based on the data in the panel packs, the presentations, and the expertise around the table. I will now read Question 1.

The FDA has identified the following risks to health of noninvasive bone growth stimulators based on available information for these devices, including the 2005

reclassification petition:

- Failure or delay of osteogenesis
- Burn
- Electrical shock
- Electromagnetic interference
- Adverse tissue reaction
- Adverse interaction with internal or external fixation devices
- Adverse biologic effects

a. Please comment on whether this list completely and accurately identifies the risks to health presented by non-invasive bone growth stimulators.

Dr. Gilbert.

DR. GILBERT: So the question of interaction, I didn't hear any real substantive discussion of that, so I'm wondering if somebody can frame quickly for me, you know, has there been evidence of that, what's the mechanism by which -- I mean are you inducing a current that generates heat? What's the concern there? Somebody describe that to me.

DR. MUIR: This is Jesse Muir, I guess I can provide a brief comment here. So generally, we looked at these devices as being used in patients that may have a number of other medical implants, medical devices in them, so ensuring that there's no cross-effect between these devices, so looking at both how the device could affect the medical efficacy of another device or how another device could affect these devices. So generally looking at could it be causing heating, dispersion of the signal. You know, these are generally tests that could be done using bench test assessment of energy signals and electromagnetic safety or heating.

DR. GILBERT: Thank you.

DR. SMITH: Dr. Graf.

DR. GRAF: In a similar fashion to what Dr. Gilbert just mentioned, the last portion of the adverse biologic effects just seems overly vague, as from everything we've looked at we haven't seen any adverse biologic effects and either that has to be better defined or, in my opinion, deleted.

DR. SMITH: Dr. Finnegan.

DR. FINNEGAN: I'm not sure how to put this in, but we've been talking about signals and different signals from what are now available and I'm wondering if there's some way we can put in here that the signal itself is not detrimental, I don't know exactly how to put that. Not so much that there's failure of what it's supposed to do, but the signal itself is not actually a problem, is non-biologic or --

DR. SMITH: Were there any other comments for part (a) of this question?

Dr. Alander.

DR. ALANDER: Maureen, could you clarify that? You're saying that you would want that put into adverse -- that there would not be any adverse reaction to the wavelengths, is that what you're saying?

DR. FINNEGAN: No, I'm more not so much worried, but there are -- if there are going to be new signals coming out, one of the question is do they or do they not work for the osteogenesis, but the other question is do they do some other -- do they have unintended consequences.

DR. ALANDER: Right.

DR. FINNEGAN: And I don't know how to put that in here, but that would be one of my concerns.

DR. ALANDER: Yeah, that might be more towards Carl's comments that, you know, we don't know everything about what the signals are doing.

DR. SMITH: Ms. Bonnell.

MS. BONNELL: I do believe that if there are concerns, that labeling and special controls would be a great mitigater for that, either recommended postoperative care or even precautions, warnings for the potential for interaction and if there were serious concerns, within the labeling you can also have a contraindication. But those are also -- I'm sorry, labeling is also within the list of recommended special controls, in terms of adequate instructions for use.

DR. SMITH: Are there any other comments for part (a) of Question 1?

(No response.)

DR. SMITH: Part (b) of Question 1: Please comment on whether you disagree with inclusion of any of these risks, or whether you believe that any other risks should be included in the overall risk assessment when considering all indications for this device type.

Are there any comments or discussion for part (b)? And I recognize that some of this we touched on when discussing part (a).

(No response.)

DR. SMITH: Captain Peat, with regard to Question 1, the Panel generally believes that there is a long history of these devices. There was some concern raised regarding if there needs to be a qualification regarding device interactions and how that would happen either based off the evidence or the mechanism of interaction. There also was concern about if adverse biologic effects should be more granularly defined. And also there were questions about the signal characteristics, specifically if the signal characteristics themselves need to be defined in a way that characterized safety and efficacy in a way that was independent from the field characteristics.

Captain Peat, is this adequate?

DR. PEAT: Yes, this is. One point of clarification. For the adverse biological effect that has more granularity in the definition or it should be deleted, is that what you heard,

as well, Dr. Smith?

DR. SMITH: Yes, Captain Peat, my understanding was that the question was either to better clarify it or to delete that from the portion.

DR. PEAT: All right, thank you. Thanks for your feedback. Thanks for that clarification, as well. This is adequate.

DR. SMITH: Thank you.

We will now move on to Question 2. And Question 2 is about a page of text, which everyone has in their packets and that I believe is -- it's also available to the public and so I'm going to read the salient portions of it, but I'm going to refrain from reading it verbatim, if that's okay with everyone.

Question 2: Section 513 of the Food, Drug, and Cosmetic Act states a device should be Class III if there's insufficient information that exists to determine that general controls are sufficient to provide a reasonable assurance of its safety and effectiveness, or that application of special controls could provide such assurance, and if in addition the device is life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury.

A device should be Class II if general controls by themselves are insufficient to provide a reasonable assurance of the safety and effectiveness, and there is sufficient information to establish special controls to provide such assurance.

A device should be Class I if general controls are sufficient, or if there's insufficient information that exists to determine that general controls are sufficient to provide a reasonable assurance of their safety and effectiveness, or establish special controls to provide such assurance, but it's not purported or represented to be for a use in supporting or sustaining human life, or for a use which is of substantial importance in preventing

impairment of human health. Additionally, it does not present a potential unreasonable risk of illness of injury for Class I.

a. Based off of those definitions, the FDA believes that general controls alone are not sufficient to provide a reasonable assurance of safety and effectiveness for noninvasive bone growth stimulators. If you disagree, please discuss how general controls alone are sufficient to provide a reasonable assurance of safety and effectiveness for this device type. General controls may include:

i. Prohibition against adulterated or misbranded devices

ii. Good manufacturing practices

iii. Registration of manufacturing facilities

iv. Listing of device types

v. Record keeping

Are there any comments for Question 2(a)?

Yes, Dr. Yang.

DR. YANG: I guess just for the record I would say that I concur with FDA's contention that general controls are not enough, are not sufficient to put this in a Class I.

DR. SMITH: Yes, Dr. Alander.

DR. ALANDER: I would agree with the FDA's conclusion.

DR. SMITH: Yes, Dr. Ebramzadeh.

DR. EBRAMZADEH: I would agree, as well, general controls are not sufficient.

MR. O'BRIEN: Well, why not? I agree, also.

DR. SMITH: Are there any other comments?

Yes, Dr. Finnegan.

DR. FINNEGAN: You need this for the record?

DR. SMITH: No.

DR. FINNEGAN: I concur that general are not, for the record.

DR. SMITH: Thank you.

DR. BALLMAN: And I also agree.

DR. PRICE: I also agree.

UNIDENTIFIED SPEAKER 1: I also agree.

DR. SMITH: I need for --

UNIDENTIFIED SPEAKER 2: I agree.

DR. SMITH: I need for the virtual meeting -- we can't all see who's raising hands. Does anyone not agree, before I move on to the next question?

(No response.)

DR. SMITH: Then I think we can concur that it's unanimous agreement on part (b) (sic).

Question 2(c): The FDA does not believe that noninvasive bone growth stimulators present a "potential unreasonable risk of illness or injury." Do you agree with this assessment? If not, please explain why.

And for Part 2(c), just as this is for the record and is being transcribed, I would like each panelist to please state their agreement or lack of agreement. And why don't we first have comments and then just for orderliness, after we have comments I'll then ask each Panel member directly so we can have everyone's response duly noted.

Mr. O'Brien.

MR. O'BRIEN: I just wanted to ask a question of clarification. I don't think we answered part (b) on the question, the first one. We answered part (a), I don't think we answered part (b).

DR. SMITH: Okay, thank you, Mr. O'Brien.

Let's go back to part (b).

Part (b). The question was the FDA does not believe that noninvasive bone growth stimulators are "life-supporting or life-sustaining, or of substantial importance in preventing impairment of human health."

I believe, Mr. O'Brien, you want us to correctly address the second part of that question, which was "of substantial importance in preventing impairment of human health."

MR. O'BRIEN: If I may, yes, I would like to address that and sometimes if it's not broke, don't fix it. But I do have to say that speaking specifically for the spine community, I know well this is a substantial issue. Without spinal deformity, surgery is a growing problem throughout the world and the amount of complications or revisions is also growing and pseudarthrosis is a major part of that, it has substantial costs both personally and societally and financially and I do think that, from that perspective, from a patient perspective, it can't be overlooked as an important impairment to human health if we have devices that, in fact, are not good adjuncts to the spinal fusion primary surgery.

DR. SMITH: Are there any other comments for the second part of 2(b)?

Yes, Dr. Alander.

DR. ALANDER: Dirk Alander. Yeah, I struggle with this because I do agree with you, Joe, that it can really impact people. At the same time, I think that the access to newer technologies are opening up that is important also and, you know, if you get a good fusion or you do good techniques, you do the best you can, sometimes I'm just trying to put that in perspective and I'm struggling with this. But I'm tending to figure that this -- I would have to agree with the FDA, but that's where I'm leaning towards.

DR. SMITH: Dr. Gilbert.

DR. GILBERT: Yeah, if I can add just a thought here. So the impairment to human health is the nonunion, right? The harm really is the nonunion. It's not that the device

generated the nonunion, it's that the device failed to correct the nonunion. So the harm is really coming from the original state, not so much the device, although it could be the device fails to correct that, that harm and that pain and that -- you know, the patient clearly suffers in the event that the union doesn't occur. So I'm trying to distinguish and I think -- so I agree with FDA here, it's not the device that's creating the nonunion, it's just failing to heal the nonunion.

DR. SMITH: Mr. O'Brien.

MR. O'BRIEN: I'd just like to follow up, you know, because what this says is lack of sufficient data and in fact, we had 30% revision rates among adult spinal deformities. We don't know, there's no study that I'm aware of that went back and said did the patients who wore the bone growth stimulators, were they significantly less of this 30% revision. So it, in fact, is that -- if we have something that doesn't perform to that, that it does cause the harm, because the one that we currently have is preventing the harm. So I would disagree with that, respectfully, but that's my view.

DR. SMITH: I would like to make a comment, I think, to the FDA. My understanding as we address this question is that it's for the indication of the patient has a nonunion. It's not for the indication of prophylaxis for a nonunion, is that correct?

DR. MUIR: So this is Jesse again. That was a question to FDA?

DR. SMITH: Yes, sir.

DR. MUIR: Yes, we are looking at indications for treatment of existing nonunions for these devices.

DR. SMITH: Yes, Dr. Gilbert.

DR. GILBERT: So just to kind of close that loop, what you're referring to are those devices that have likely gone through a PMA for approval for use for these circumstances, so those are ones that have already gone through the most rigorous and there's still a

question raised in your mind. And that's absolutely legitimate. The question I would have is would keeping them in Class III answer that, you know, address that question?

UNIDENTIFIED SPEAKER: Well, if Class III didn't do it, I don't think Class II is going to.

DR. SMITH: Are there any additional comments for part 2 of Question (b)?

Yes, Ms. Bonnell.

MS. BONNELL: I might ask ourselves to liken the question to any other traditional fixadent (ph.) in that, if that a traditional fixation device were unable to perform as intended, resulting in nonunion, we would expect that there were mitigaters in place to reduce the risk of that occurring and that through verification and validation and performance testing that we would have predicted outcomes. And so I agree with the prior comment that this question is more about the outcome or the unforeseeable outcome versus what is it that we can mitigate in terms of control.

DR. SMITH: Are there any other comments before we state our respective, for lack of a better word, votes for part 2 of Question 2(b)?

(No response.)

DR. SMITH: For this component I don't sense that there is a consensus opinion and so I would like -- I'll go through the names of each member on the Panel and then ask that you each state your answer to the second portion of Question 2(b), and we'll start with Dr. Gilbert.

DR. GILBERT: I agree with FDA.

DR. SMITH: Dr. Finnegan.

DR. FINNEGAN: I agree with the FDA.

DR. SMITH: Dr. Graf.

DR. GRAF: I agree with the FDA.

DR. SMITH: Dr. Ebramzadeh.

DR. EBRAMZADEH: I agree with the FDA.

DR. SMITH: Dr. Alander.

DR. ALANDER: Agree with the FDA.

DR. SMITH: Dr. Price.

DR. PRICE: I agree.

DR. SMITH: Dr. Ballman.

DR. BALLMAN: I agree with the FDA.

DR. SMITH: Dr. Elder.

DR. ELDER: I agree with the FDA.

DR. SMITH: Ms. Bonnell.

MS. BONNELL: I also concur for Question 2(b), I agree with the FDA.

DR. SMITH: Dr. Pfeffer.

DR. PFEFFER: Agree.

DR. SMITH: Dr. Yang.

DR. YANG: Agree with the FDA.

DR. SMITH: Mr. O'Brien. Excuse me, Mr. O'Brien, your microphone's muted.

MR. O'BRIEN: I'll stand up and say I don't agree, but thank you.

DR. SMITH: Thank you.

We'll move on to Question 2(c). FDA does not believe that noninvasive bone growth stimulators present a "potential unreasonable risk of illness or injury." Do you agree with this assessment? If not, please explain why.

Dr. Gilbert.

DR. GILBERT: Well, I guess I would rely back on the decades of use and the very small incidences of reported injury or illness arising from the use of these devices. That clinical use over decades, I think, speaks to this question, so I agree with the FDA on this.

DR. SMITH: Mr. O'Brien.

MR. O'BRIEN: I agree with the FDA, I do not think there's unreasonable risk for injury.

DR. SMITH: Dr. Ebramzadeh.

DR. EBRAMZADEH: I agree with the FDA.

DR. SMITH: Dr. Alander.

DR. ALANDER: Agree with the FDA.

DR. SMITH: Dr. Finnegan.

DR. FINNEGAN: I agree with the FDA.

DR. SMITH: And I will call out names of other Panel members.

Dr. Graf.

DR. GRAF: I agree with the FDA.

DR. SMITH: Dr. Price.

(No response.)

DR. SMITH: Dr. Price, are you able to hear us?

DR. PRICE: I agree with the FDA.

DR. SMITH: Dr. Ballman.

DR. BALLMAN: I agree with the FDA.

DR. SMITH: Dr. Elder.

DR. ELDER: I agree with FDA.

DR. SMITH: Ms. Bonnell.

MS. BONNELL: With respect to Question 2(c), I also agree.

DR. SMITH: Dr. Pfeffer.

DR. PFEFFER: Agree.

DR. SMITH: Dr. Yang.

DR. YANG: Agree.

DR. SMITH: And just because this is a virtual meeting, is there anyone that has another comment before we move on to Question 2(d)?

(No response.)

DR. SMITH: Question 2(d): FDA believes sufficient information exists to establish special controls for noninvasive bone growth stimulators. Based on the information presented today, please discuss whether you believe that sufficient information exists to establish special controls that can provide a reasonable assurance of safety and effectiveness for this device type.

Are there any comments or -- yes, Dr. Finnegan.

DR. FINNEGAN: So a question for the FDA. It is my understanding that with the Class II you're going to ask for an IDE for any new proposals.

DR. MUIR: So this is Jesse Muir. Even for Class III or Class II devices, we cannot request an IDE necessarily, but we would be requesting clinical evidence. For any device where clinical evidence is needed, this could include an OUS study which would not include necessarily an IDE.

DR. FINNEGAN: All right, so clinical efficacy would be part of the proposal?

DR. MUIR: Yes. So clinical evidence is part of the special controls.

DR. FINNEGAN: Okay.

DR. SMITH: Before we go -- and I'll call off names for the votes. We had a technology issue with the webcast.

Dr. Osborn, with respect to the past two questions, parts 2(a) and 2(b) and 2(c), could you please, for the record, indicate your opinion?

DR. OSBORN: Yes, I agree with the FDA. Thank you.

DR. SMITH: And if there is no further comments for part 2(d), I'm going to read off

the names of the voting members of the Panel and ask for your input.

Dr. Gilbert.

DR. GILBERT: For 2(d), I agree with the FDA.

DR. SMITH: Dr. Finnegan.

DR. FINNEGAN: I agree with the FDA.

DR. SMITH: Dr. Graf.

DR. GRAF: I also agree with the FDA.

DR. SMITH: Dr. Ebramzadeh.

DR. EBRAMZADEH: I agree with the FDA.

DR. SMITH: Dr. Alander.

DR. ALANDER: I agree with the FDA.

DR. SMITH: Dr. Ballman.

DR. BALLMAN: I agree on 2(d) with the FDA.

DR. SMITH: Dr. Elder.

DR. ELDER: I agree with the FDA.

DR. SMITH: Dr. Pfeffer.

DR. PFEFFER: Agree.

DR. SMITH: Dr. Yang.

DR. YANG: Agree with the FDA.

DR. SMITH: Dr. Osborn.

DR. OSBORN: I agree with the FDA.

DR. SMITH: Mr. O'Brien.

MR. O'BRIEN: I agree with the FDA.

DR. SMITH: Captain Peat, with regard to Question 2, the Panel generally agreed that for Question 2(a).

DR. PEAT: I found this information to be adequate. Thank you.

DR. SMITH: Thank you. For Question 2(b) there was unanimous agreement on the first portion of the question. For Question 2(b), the Panel generally agreed, although some members of the Panel did have some concerns and did not agree and this discussion focused primarily upon concerns about if the indications of the device are to treat an established nonunion or if the relative medical benefit of the device and potentially preventing a nonunion should be weighed in the consideration. For Question 2(c) there is unanimous agreement with the FDA, and for Question 2(d) there was unanimous agreement with the FDA.

Captain Peat, is this adequate?

DR. PEAT: This information is quite adequate and thank you so much for the robust discussions.

DR. SMITH: We will now move on to Question 3. And again, Question 3 has a lot of text.

Captain Peat, as Question 3 is available to the Panel members and the public, do you wish me to read into the record all of the text and the definitions or may I just read into the record the bolded portion of the specific question?

DR. PEAT: I would truncate it, so the bolded portion, since everyone has the information at hand.

DR. SMITH: Thank you, Captain Peat.

DR. PEAT: Um-hum.

DR. SMITH: With respect to Question 3, please discuss whether these special controls appropriately mitigate the identified risks to health of this device type, and whether you recommend additional or different special controls.

Dr. Gilbert.

DR. GILBERT: I sort of raised this earlier about the question of postmarket surveillance and whether that might be included as a special control. And so maybe a question to FDA, what's the -- is there any sort of precedent or conditions that you would consider that to be an important step or not to take with a device of this sort?

DR. MUIR: So this is Jesse Muir. I think when we look at requirements for special controls, we often would look at this on a case-by-case basis depending on the level of evidence we have and any unanswered questions that we would need to see answered in the postmarket.

DR. SMITH: Dr. Finnegan.

DR. GILBERT: I would recommend maybe consideration of adding something like that to this.

DR. FINNEGAN: So I'd like to just support Dr. Gilbert's point, I think it might help with those people who are concerned about it not being a level -- a Class III. If, in fact, there was postmarket surveillance, I realize this increases cost a little bit, but it might help alleviate some of the concerns about figuring out the efficacy.

DR. SMITH: Dr. Alander.

DR. ALANDER: I would support that and it's very important.

DR. SMITH: Dr. Price.

DR. PRICE: I also support that.

DR. SMITH: Mr. O'Brien.

MR. O'BRIEN: I would support that, as well.

DR. SMITH: Dr. Elder.

DR. ELDER: Yeah, I would support that, as well, and I wanted to add also that I think we need to be very rigorous in terms of the clinical data for the special controls and hold them to a higher standard than some of the other clinical data that's been required,

especially looking at fusion status and that with more modern techniques, including CT scan and test bone fusion and trying to insist on at least 1 year of follow-up, if not 2 years like some of the other studies, if required. And I'm looking, as well, at other factors that can determine fusion rates, osteoporosis, and looking at broad health optimization as well as smoking cessation in comparison to different forms of the device, as well.

DR. SMITH: Dr. Yang.

DR. YANG: I'd like to see a little bit more than just the labeling as a special control for interactions with other implanted medical devices only because with the current technology and all of that, new devices are coming -- new implantables are coming out at all times, so I think that interactions with existing implantables is something that deserves a little bit more attention.

DR. SMITH: Dr. Ebramzadeh.

DR. EBRAMZADEH: With regard to the proposed postmarket surveillance, what's the difference between that and item 1, which says, "Clinical performance data must support the intended use of this product"?

DR. SMITH: Dr. Gilbert.

DR. GILBERT: Just my opinion and my view of this, Eddie, is that performance data would need to be submitted and accepted by FDA prior to the marketing of the device and what I'm suggesting is beyond that, once it's in the stream of commerce, that there would be some follow-up assessment of the performance of the device on the market.

DR. SMITH: Are there any other comments for Question 3?

(No response.)

DR. SMITH: Captain Peat, with regard to Question 3, the Panel generally believed that some degree of postmarket surveillance was indicated. Specifically, there was concern about postmarket surveillance, there was concern about the need for at least 1-year follow-

up. Also, concern was raised regarding special controls with respect to potential interference with other devices, particularly as other devices may be introduced in the near future. Also, there was concern regarding the need for quantifiable performance data and then follow-up after postmarketing.

Captain Peat, is this sufficient?

DR. PEAT: Thank you for your recommendations.

DR. SMITH: Thank you.

At this point I would like to ask our representatives if they had any additional comments. We will start with our Consumer Rep. Ms. Price, do you have any comments?

DR. PRICE: No. Thank you.

DR. SMITH: Thank you.

I would like to ask our Industry Rep if she had any additional comments. Ms. Bonnell, do you have any comments?

MS. BONNELL: No substantive comments to the discussion, just my compliments to the Panel for looking at it from all angles and coming to a very appropriate and least burdensome decision, so thank you.

DR. SMITH: Thank you, Ms. Bonnell.

I would like to see if our Patient Rep has any additional comments. Mr. O'Brien, do you have any comments?

MR. O'BRIEN: Thank you, Dr. Smith. No, I've made my comments. I appreciate the work that the FDA has done and the work of all the panelists and the thought for the patients who are the ultimate end result of everything that we do here and that, to me, is the ultimate outcome, is what happens to the patients when they walk away, so all of these things. And I appreciate your concern and thought regarding that.

DR. SMITH: Thank you, Mr. O'Brien.

We will now hear final summations from the FDA. Captain Peat, you have the floor.

DR. PEAT: Thank you, Dr. Smith. FDA does not have any additional information to present at this time. FDA has requested the Panel's input on a proposal to regulate these devices as Class II with special controls and we will take into consideration your recommendations.

I wanted to audibly thank the panelists for taking time out of your busy schedules to participate and for the robust discussions in the reclassification for noninvasive bone growth stimulator devices, as well as the classification of preamendment devices for facet screw systems. It is not lost on us that this is a unique period that we're actually doing all of this virtually, but I agree with Mr. O'Brien in the sense that we're all here for our patients and we've done a good job today for the American public. Thank you.

DR. SMITH: I would like to thank the Panel, the Open Public Hearing speakers, and the FDA for their contributions to today's panel meeting.

Lieutenant Commander Miller has some final remarks. Lieutenant Commander Randoshia Miller obtained her M.S. from the University of Maryland and BSN from Clemson University. She has been at the FDA for nearly 4 years and is currently the regulatory health project manager within the Office of Orthopedic Devices.

Lieutenant Commander Miller, you may proceed.

DR. PEAT: Before we go into Lieutenant Commander Miller's presentation, I just want to let you know that yesterday she departed for Hawaii, she's actually on deployment for COVID-19, so I really want to thank her for all of her hard work all of the way up to this particular day while she's actually deploying for an underserved population.

LCDR MILLER: Good afternoon, everyone. My name is Lieutenant Commander Randoshia Miller and on behalf of the Office of Health and Technology Division 6, we would like to thank you for joining our Orthopaedic and Rehabilitation Devices Panel meeting for

Day 1. We would like to thank all Panel members, presenters, and FDA staff that worked so hard to implement this panel meeting, all while being 100% virtual. Please join us for our second day of the panel meeting tomorrow at 8:00 a.m. Eastern Standard Time. Have a great rest of the day. Thank you.

DR. SMITH: I now pronounce the September 8th session of the Orthopaedic Devices Panel of the Medical Devices Advisory Committee adjourned.

(Whereupon, at 2:37 p.m., the meeting was adjourned.)

3541

C E R T I F I C A T E

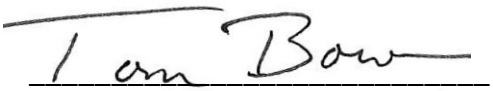
This is to certify that the attached proceedings in the matter of:

ORTHOPAEDIC AND REHABILITATION DEVICES PANEL

September 8, 2020

Via Webcast

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.



TOM BOWMAN

Official Reporter

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947