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 MEDICAL DEVICES ADVISORY COMMITTEE
 + + +
 ORTHOPAEDIC AND REHABILITATION DEVICES PANEL

May 22, 2013
 8:00 a.m.

Holiday Inn
 2 Montgomery Village Avenue
 Gaithersburg, Maryland

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MEETING

(8:03 a.m.)

DR. KELLY: I would like to call this meeting of the Orthopaedic and Rehab Devices Panel to order. It is now approximately 8:03 a.m. I am John D. Kelly, IV, Chairperson of this Panel. I am a sports shoulder specialist at the University of Pennsylvania.

I note for the record that the voting 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 regulation.

For today's agenda, the Panel will discuss and make recommendations on information related to the reclassification of pedicle screw spinal systems.

Before we begin, I'd like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and your affiliation. I would like to start at this end of the table.

MR. MELKERSON: I'm Mark Melkerson. I'm the Director of the Division of Orthopaedic Devices. I'm also the Acting Director of the Division of Surgical Devices, and I'm a biomedical engineer by training.

DR. DO: Good morning. I'm Huy Do. I am a Professor of Radiology and Neurosurgery at Stanford University. I'm a neuroradiologist

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and interventional neuroradiologist practicing at Stanford.

DR. GRAF: I'm Dr. Carl Graf. I'm an orthopaedic spinal surgeon with the Illinois Spine Institute in Chicago, Illinois.

DR. LEHMAN: Good morning. I'm Ron Lehman. I'm the Chief of Pediatric and Adult Spine at Walter Reed here in Bethesda, Maryland.

DR. PFEIFER: Bernard Pfeifer, orthopaedic surgeon, spine and total joints, Lahey Clinic, now emeritus, retired as of the 1st of May.

DR. ROHR: I'm Bill Rohr. I'm an orthopedic surgeon, trained also as an engineer, in private practice in Northern California, also formerly an executive of several medical device companies. Private practice again, in Northern California and specialize mostly in total joints, mostly revisions, and complex hand surgery.

DR. GOLISH: I'm Raymond Golish. I'm an orthopedic surgeon, fellowship-trained spinal surgeon, and my Ph.D. is in engineering. My research experience is in devices, biologics, imaging, and clinical trials and data analysis. I'm a member of the American Academy of Orthopaedic Surgery's Biomedical Engineering Committee, and ASTM F04.25 working group. Some of the professional societies like the Academy I'm affiliated with, and they submit information to this Panel, and I recuse myself from my role in those panels.

LCDR ANDERSON: I'm Lieutenant Commander Sara Anderson. I'm the DFO, and I'm representing FDA and the United States Public Health

Service.

DR. POTTER: Hollis Potter. I'm Professor of Radiology at Cornell Medical School. I run the MRI Department at the Hospital for Special Surgery where I hold the Coleman Chair in MRI Research.

DR. HAINES: I'm Steve Haines. I'm a professor and Chair of Neurosurgery at the University of Minnesota.

DR. LYMAN: Stephen Lyman, Associate Professor of Public Health at Weill Cornell Medical College and Division of Outcomes and Effectiveness. Also the Director of Epidemiology and Biostatistics at the Hospital for Special Surgery.

DR. TRIER: My name is Kathy Trier, and I work at Corin USA. I am serving on this Panel as the Industry Representative. I have a number of years in orthopedics regulatory and clinical research at the university and also in industry.

MR. O'BRIEN: My name is Joe O'Brien. I'm president and CEO of the National Scoliosis Foundation. I am also a spine deformity patient. I've had four surgeries. I'm fused from T4 to L5, including pedicle screws, hooks, and two Harms cages. I'm one of 14 members with spinal deformity, including spondylolisthesis and degenerative disc disease.

MS. WHITTINGTON: My name is Connie Whittington. I'm the Chief Nursing Officer at Peachtree Orthopaedic Clinic in Atlanta. I have over 35 years experience as an orthopedic nurse in the operating room, in a clinic,

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and in a hospital scenario. And I appreciate representing the consumer on this Panel.

DR. KELLY: Thank you, Panel members. If you have not done so already, please sign the attendance sheets that are on the table by the doors. At this point, Lieutenant Commander Anderson, the Designated Federal Officer for this meeting will make some introductory remarks.

LCDR ANDERSON: 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 (FACA) of 1972. With 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 on 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 laws. Under 18 U.S.C. 208, Congress has authorized FDA to grant waivers to special

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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 discussion of today's meeting, members and consultants of this Panel have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or 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, the Panel will discuss and make recommendations regarding the 515(i) order issued by FDA on April 9th, 2009, Docket No. FDA-2009-M-0101, for one of the remaining pre-amendment Class III devices, pedicle screw spinal systems, intended to treat degenerative disc disease and spondylolisthesis, other than severe spondylolisthesis grade 3 and 4 and L4-S1, or degenerative spondylolisthesis with objective evidence of neurologic impairment.

The discussion will involve making recommendations regarding regulatory classification to either confirm to Class III subject to PMA or reclassify to Class I or Class II, subject to 510(k), as directed by Section 515(i) of the Food, Drug and Cosmetic Act. Pedicle screw spinal systems are

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posterior spinal screw and rod systems intended as an adjunct to fusion for the treatment of degenerative disc disease, trauma, deformity, failed previous fusion, tumor, infection, and inflammatory disorders of the thoracolumbar spine. This meeting is classified as a particular matter with general applicability.

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 connection with 18 U.S.C. Section 208. A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Dr. Kathy Trier is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Corin USA.

We would like to remind members and consultants that if the discussion involves any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants needs 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 that they may have with any firms at issue.

Thank you.

Before I turn the meeting back to Dr. Kelly, I'd like to make a few general announcements.

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Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated, telephone 410-974-0947. Information on purchasing videos of today's meeting can be found on a table outside the meeting room.

The press contact for today's meeting is Susan Laine.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area behind the speakers' podium. I request that reporters please wait to speak to the FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing today and have not previously provided an electronic copy of your slide presentation to FDA, please arrange to do so with Mr. James Clark at the registration table.

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

Finally, please silence your cell phones and other electronic devices at this time.

Thank you very much. Dr. Kelly.

DR. KELLY: Thank you, Lieutenant Commander Anderson.

I would like at this point to introduce Ms. Marjorie Shulman, Director of the Premarket Notification 510(k) Program at the FDA, who will be providing a classification overview to the Panel.

MS. SHULMAN: Good morning. Welcome back. For those of

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you who heard this yesterday, I'm sorry.

(Laughter.)

MS. SHULMAN: I'm going to give a general overview of what we are doing and why we're here today. So the purpose of the meeting is to provide input on the classification of pre-amendment devices and whether we should -- whether the FDA should call for PMAs or reclassify into Class I or Class II.

What is a pre-amendment device? It's a type of device that is introduced into interstate commerce prior to May 28th, 1976, the enactment date of the Medical Device Amendments.

So the classification process that we're going to follow, recent legislation, FDASIA that was passed last summer, has affected the classification of medical devices, including the Class III 510(k)s, and FDA must now publish a proposed order announcing our proposed classification and seek public comment, hold a panel meeting if classifying or reclassifying the device type, consider comments and all available information, including panel recommendations, prior to issuing a final order classifying -- finalizing the classification of the device.

So the different classes that we have, Class I, II, and III, it's based on the controls necessary. And a device should be placed in the lowest class whose level of control provides reasonable assurance of safety and effectiveness. Class I is general controls, Class II is general and special

controls, and Class III is premarket approval.

General controls include such things as prohibition against adulterated or misbranded devices, good manufacturing practices, registration of the manufacturing facility, listing of the device type that's made there, and record keeping of repair, replacement, refund, et cetera. Special controls include performance standards, postmarket surveillance, patient registries, and development and dissemination of guidelines.

Class I devices are for devices which general controls are sufficient to provide reasonable assurance of the safety and effectiveness, and Class I devices typically do not require a 510(k) review. They're exempt from 510(k).

There's also another part of Class I for devices that cannot be classified into Class III because they're not life-sustaining or life-supporting or of substantial importance in preventing impairment of public health, and they do not present a potential unreasonable risk of illness or injury. They also cannot be classified into Class II because insufficient information exists to establish special controls to provide reasonable assurance of the safety and effectiveness. Some examples of Class I devices include general manual orthopedic surgical instruments, adhesive bandages, manual wheelchairs, and crutches.

Class II devices are for devices that cannot be classified in Class I because general controls are insufficient to provide reasonable assurance of

the safety and effectiveness, and there is sufficient information to establish special controls to provide the assurance. Class II devices typically require premarket notification submitted to FDA prior to being marketed, although Class II devices can be exempt. Some examples of Class II devices include cages, resorbable bone void fillers, powered wheelchairs, and powered muscle stimulators.

So how are special controls used? For an example, cages were reclassified from Class III to Class II special controls. FDA issued a special controls guidance document -- guidance to mitigate the risk to health, and it included such things as biocompatibility testing, material characterization, mechanical testing, sterility, and labeling, which included warnings, precautions, adverse effects, et cetera. These special controls in combination with the general controls provide reasonable assurance of the safety and effectiveness. And companies must provide evidence in their 510(k) submission of how the special controls were addressed.

Class III is for devices that cannot be classified into Class I or II because insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness, and the devices are life-sustaining and/or life-supporting, or of substantial importance in preventing impairment of human health, or present an unreasonable risk of illness or injury. Class III devices typically require premarket approval, PMA, prior to being marketed. Some examples of Class

III devices include such devices as total artificial disc replacement, stair climbing wheelchairs, and implanted neurostimulators.

So what are Class III 510(k) devices? Those are pre-amendment devices where FDA issued a proposed rule classifying them as Class III, however, no rule -- no final rule was issued, or a final rule was issued for Class III, but the rule did not contain a date by which companies were required to submit a PMA. Therefore, these Class III devices are allowed to proceed to market via the 510(k) process until such time as either a call for PMAs or a reclassification is finalized.

So what is the process we're going to follow? We can reclassify a pre-amendment device in a proceeding that paralleled the initial classification proceeding that was one in the late '70s, early '80s, or based upon new information respecting a device either on FDA's own initiative or upon a petition of an interested person, and the Agency classifies or reclassifies intended uses which have actually been reviewed by the Agency.

So here's a flowchart to help you out. The first step that's not on the flowchart would be: are general controls sufficient to provide reasonable assurance of safety and effectiveness. The next questions we're going to ask: is it life-sustaining or of substantial importance in preventing impairment of human health, or potential unreasonable risk of illness or injury. If the answers to those are no, and there's sufficient information for special controls and the answer to that is no, that can go into that Class I that

I discussed earlier. If there is potential risk or life-sustaining or life-supporting, but there is sufficient information for special controls, then if the answer to that is yes, that can go into Class II. If the answer to that is no, that would be Class III.

So what we need from the Panel is input on the classification of the devices that are the subject of the Panel session today. The input should include an identification of risk to health, if any, presented by the device; whether the device is life-supporting/life-sustaining; of substantial importance in preventing impairment to human health; or present an unreasonable risk of illness or injury. Also, whether sufficient information exists to develop special controls, and the identification of the special controls.

After this Panel meeting, FDA will issue a proposed order proposing the classification of the device and seeking public comment on the proposal. FDA may propose that the device be reclassified or remain in Class III and call for PMAs, or split the reclassification -- split the classification based on indication or technology. FDA will consider the available evidence, including the input of this Panel and public comments. FDA will issue a final order identifying the appropriate class. If Class I or Class II, devices may continue to be marketed. If Class III, existing devices will remain on the market, but must submit a PMA by a specified timeframe to continue marketing. If the PMA is not approved, devices will be considered

misbranded and must be removed from distribution. Thank you.

DR. KELLY: Thank you, Ms Shulman. I'd like to thank you again. You've given this talk so many times, I bet you've memorized it by now, haven't you?

MS. SHULMAN: I have.

DR. KELLY: Does anyone on the Panel have a brief clarifying question for Ms. Shulman?

Okay. Very well. Thanks again.

I would like to invite at this point the FDA to the podium to begin their presentation. First, representing the FDA is Dr. Katherine Kavlock. The FDA will have 60 minutes for their presentations.

DR. KAVLOCK: Good morning, distinguished Panel members, members of industry, and audience members. Thank you for being here this morning. My name is Kate Kavlock. I'm a biomedical engineer and reviewer in the Anterior Spine Devices Branch in the Office of Device Evaluation. I'll be starting the FDA presentation on the 515(i) order for pedicle screw spinal systems for certain indications for use.

The purpose of this Panel meeting is to discuss the available scientific evidence and to make recommendations to the FDA regarding the classification of thoracolumbosacral pedicle screw spinal systems for certain indications for use.

This morning we will be discussing several topics, including a

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brief device description along with the regulatory history of pedicle screw systems. We will discuss the relevant clinical background and associated targeted literature review. A representative of our Office of Surveillance and Biometrics will present a full systematic review of the available literature for the treatment of degenerative disc disease, or DDD, using pedicle screws. We will also be presenting information on a subset of devices known as dynamic stabilization systems, as well as the adverse event analysis conducted using our MAUDE database. Finally, we will present the risk to health and our proposed special controls to mitigate these risks.

During our discussion of these sections, several questions for the Panel will be highlighted, and at this time the Panel is not going to be commenting on these questions. We are just providing them within the context of the relevant information. The questions will be asked separately this afternoon.

The FDA team members involved with the review of the classification materials as well as the literature analysis, are acknowledged here.

I will briefly introduce you to the scope of this Panel meeting and provide you with a brief device description and a snapshot of the regulatory history surrounding the use of pedicle screw spinal systems.

Specifically, the Panel will be asked to provide input on the FDA's proposed classification strategy for pedicle screw spinal systems for use

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in the thoracolumbosacral spine for treatment of DDD and types of spondylolisthesis other than severe spondylolisthesis (grades 3 or 4) or degenerative spondylolisthesis with objective evidence of neurologic impairment into Class II special controls. It should be noted that this classification regulation is currently split between Class II and Class III.

Although the focus of this Panel today is primarily on 21 C.F.R. 888.3070(b)(2) of the classification regulation as that is the part of the classification process that has not been completed, it should be noted that some elements of the discussion may be relevant to modifications that could eventually impact Part (b)(1). Any modifications to Part (b)(1) of the regulation are subject to a different regulatory process.

Nearly all pedicle screw spinal systems consist of anchor points via screws, which can be supplemented by hooks or wires, longitudinal members that can be rods, plates, and/or hybrid rod/plate configurations, and optional transverse connectors, which serve as the cross-linking elements for the longitudinal members.

The scope of the 515(i) order and this Panel meeting includes both traditional rigid pedicle screw spinal systems containing uniform metallic rods as well as a subset of these systems considered to be dynamic stabilization systems. Dynamic stabilization systems contain non-rigid, non-uniform, or non-metallic rods, or contain components such as polymer cords, movable screw heads, or springs. For each device type, the Panel will

discuss the cleared indications for use, the risk to health, the available safety and effectiveness information, and proposed special controls.

The regulatory history of pedicle screw spinal systems dates back to the early 1990s. The first classification panel meetings were held in 1993 and 1994 to discuss the concept and results of a historical cohort study, which provided clinical information on the use of pedicle screw fixation in thoracic lumbar and sacral fusions, and which we reference later during the clinical portion of our presentation. Specific risks to health were also identified and discussed at these panel meetings.

Subsequent to the panel's recommendation, a proposed rule was published in 1995, followed by comments that were addressed with the final rule classifying pedicle screw use in the thoracolumbosacral spine as Class II devices, with the exception of the patient populations with DDD and spondylolisthesis other than degenerative spondylolisthesis with objective evidence of neurologic impairment.

In 2001, a technical amendment was published to correct the omission of one intended use: the use of pedicle screw spinal systems in the treatment of severe spondylolisthesis (grades 3 and 4) at the L5-S1 level. The technical amendment also clarified that the use of pedicle screws in a skeletally immature population as well as cervical uses remained unclassified. However, it is now understood that the pediatric uses of pedicle screw spinal systems were cleared through the 510(k) regulatory process prior to the

issuance of the 2001 technical amendment, resulting in a classification decision that designated such systems for these uses as Class II.

The Panel will be asked to comment on whether skeletally mature or skeletally immature terminology is an adequate qualification or whether such a qualification is necessary in the indications for use.

This brings us back to the purpose of this Panel meeting. In April 2009 the FDA issued the 515(i) order requesting safety and effectiveness information for the remaining pre-amendment Class III 510(k) device types to determine appropriate classification. Included within this call for information were pedicle screw spinal systems for certain uses. FDA received responses to the 515(i) order from 20 device manufacturers either individually or collectively as part of the response submitted by the Orthopedic Surgical Manufacturers Association or OSMA.

The respondents unanimously recommended reclassification of pedicle screw spinal systems used as an adjunct to fusion for the treatment of DDD and the remaining Class III types of spondylolisthesis into Class II. Certain respondents did not limit their reclassification recommendations to the pedicle screw uses described in 21 C.F.R. 888.3070(b)(2). For example, several manufacturers recommended that the use of pedicle screws in the cervical spine and the use of pedicle screws for the treatment of pediatric deformities also be classified as Class II. Additionally, one sponsor recommended revising the regulatory definition of DDD.

I will now defer to my colleague, Dr. Vincent Devlin, who will present the clinical background and targeted literature review.

DR. DEVLIN: Good morning. I'm Dr. Vincent Devlin, an orthopedic spine surgeon and FDA medical officer in the Posterior Spine Devices Branch.

The use of pedicle screw spinal systems is the standard of care when posterior fixation and fusion of the spine is performed. Pedicle screw spinal systems offer many advantages compared to other fixation options, including hooks, wires, and cables.

The specific implant systems considered in this presentation are pedicle screw spinal systems, which utilize rigid longitudinal members and are intended for fusion. The longitudinal members may consist of a plate or more commonly a rod.

The focus of this presentation concerns the indications for pedicle screw spinal system use currently considered as Class III. Pedicle screws are regulated as Class II devices for specific indications. However, pedicle screws are currently considered as Class III when used for treatment of other spondylolisthesis and degenerative disc disease. Other spondylolisthesis is defined as spondylolisthesis other than severe spondylolisthesis, grade 3 or 4 at L5-S1, or degenerative spondylolisthesis with objective evidence of neurologic deficit.

Spondylolisthesis is defined as anterior displacement of one

vertebra in relation to the subjacent vertebra and may occur due to different disease processes. Severity of spondylolisthesis is defined according to a grading system, which quantifies the amount of translation of the superior vertebra in relation to the subjacent vertebra. Grade 1 and grade 2 spondylolisthesis are considered low grade and exhibit slippages less than or equal to 50%. Grade 3 and grade 4 spondylolisthesis are considered high grade or severe and exhibit slippages greater than 50%.

A universally accepted classification for spondylolisthesis does not exist. Wiltse, Newman, and others popularized the classification, which distinguished various types. This classification highlighted the importance of the pars interarticularis, the portion of the lamina which connects the superior and inferior articular processes.

Marchetti and colleagues stratified spondylolisthesis into two major subgroups, developmental and acquired, based on the presence or absence of dysplasia or abnormal tissue development at the level of slippage. They emphasized that the pars defect was an anatomic feature, which could not be used to distinguish between developmental and acquired spondylolisthesis types.

Degenerative spondylolisthesis is the most common type of spondylolisthesis in adult patients. It occurs as a consequence of degenerative changes, which involve the intervertebral disc space and facet joints, most commonly at the L4-5 level. Severity is limited to grade 1 or

grade 2 slippage since the intact posterior bony elements prevent slippage beyond 50%. Note that use of pedicle screw spinal systems is considered as Class II for degenerative spondylolisthesis.

The next most common type of spondylolisthesis is broadly classified as the isthmic type due to the identification of a pars defect and occurs most frequently at the L5-S1 level. Note that use of pedicle screw spinal systems is considered Class II for high grade or severe isthmic spondylolisthesis, but currently considered as Class III for treatment of low-grade isthmic spondylolisthesis.

Developmental or dysplastic spondylolisthesis includes a spectrum of patients. The extent of the developmental deficiency at the L5-S1 level determines severity of the deformity. Grade 1 and grade 2 slips result from abnormalities predominantly affecting the facet joints. These low-grade slips may present with severe central stenosis due to the presence of an intact lamina and pars interarticularis.

Grade 3 and grade 4 spondylolisthesis are the end result of severe dysplasia, which involves not only the facet joints and pars region, but in addition may involve the superior sacrum as well as the L5 vertebral body leading to the most severe spinal deformities. Note that use of pedicle screw spinal systems is considered Class II for high-grade dysplastic spondylolisthesis, but is currently considered as Class III for treatment of low-grade dysplastic spondylolisthesis.

Post-surgical spondylolisthesis most commonly develops as a result of removal or compromise of bone or soft tissue structures during posterior spinal decompression procedures. Spondylolisthesis may also occur as a consequence of trauma or pathologic processes involving the posterior spinal elements, such as spinal tumors.

As discussed, FDA currently considers use of pedicle screw spinal systems as Class II for all grades of spondylolisthesis. However, FDA also currently distinguishes certain other types of spondylolisthesis as Class III indications for use of pedicle screw spinal systems. This group of other spondylolisthesis consists of grade 1 and grade 2 nondegenerative spondylolisthesis. Low grade isthmic spondylolisthesis is the largest category contained in this Class III group.

The second area for discussion today relates to the use of pedicle screw spinal systems in the treatment of degenerative disc disease, currently referred to as DDD.

Lack of consensus exists regarding the definition and classification of the condition referred to as degenerative disc disease. Its pathophysiology and treatment remain incompletely understood. The Panel will be asked to address appropriate terminology for description of degenerative spinal conditions and to discuss limitations associated with use of the term DDD.

At each level of the spine, the articulation between adjacent

vertebrae consists of the intervertebral disc and two posterior facet joints supported by surrounding ligaments and muscles. Pathology which adversely affects the disc may also influence the facet joints. Subsequent degeneration may involve all components of the spinal motion segment.

Morphologic changes associated with disc degeneration include tears in the disc's outer covering or annulus, loss of water content in the inner region or nucleus, disc space narrowing, changes in the vertebral endplates, osteophyte formation, and annular bulging or herniation. Compression of adjacent neurostructures may also occur.

Degenerative changes may also develop in the posterior spinal column and negatively affect spinal function. Degeneration may involve the facet joints and lead to capsular laxity, facet joint instability, facet hypertrophy, and encroachment upon adjacent neurostructures.

As the process termed degenerative disc disease progresses over time, multiple spinal segments may become involved. Some individuals proceed along a pathway in which the spinal column stabilizes itself through mechanisms, which include the formation of osteophytes. Other individuals proceed along a different pathway, which may lead to spinal stenosis, spondylolisthesis, or complex spinal deformities.

Regulatory definitions for degenerative disc disease are variable and rely on combinations of clinical symptoms, physical findings, and imaging modalities. These definitions consider degeneration involving

various components of the spinal motion segment, including the intervertebral disc, vertebral endplates, ligamentum flavum, facet joints, and facet joint capsules. Regulatory definitions for degenerative disc disease invariably include patients with grade 1 degenerative spondylolisthesis and may or may not include patients who have undergone prior spine surgery.

The wide range of anatomic structures considered within the definition of degenerative disc disease is reflected in FDA guidance documents, which consider degeneration of various components of the spinal motion segment, including the facet joints and ligamentum flavum within the definition of DDD. Lack of specificity surrounding the definition of degenerative disc disease has also been reflected in the inclusion and exclusion criteria in various FDA spinal device studies.

The focus of this Panel meeting is discussion of the available evidence relating to the use of pedicle screw spinal systems for treatment of DDD in the regulatory context. This Panel meeting is not intended to discuss comparative effectiveness of alternative treatments for DDD. FDA recognizes that many factors which influence outcomes regarding treatment of DDD fall outside FDA's authority and lie within the scope of practice of medicine.

A targeted literature review related to lumbar fusion using pedicle screw spinal systems for treatment of indications currently considered as Class III was performed for the period between 1994 and 2013. Its search strategy and terms were consistent with those identified in a

literature review previously submitted to FDA by OSMA. Available safety and effectiveness data was analyzed and compared to the historical cohort study. Note that the historical cohort study provided the clinical data utilized to support classification of pedicle screws in relation to the 1993 and 1994 FDA Panel meetings.

The fusion procedures considered in this analysis included posterolateral fusion with or without use of pedicle screw spinal systems and use of pedicle screw spinal systems in conjunction with interbody fusion. The types of interbody fusion procedures considered included TLIF, or transforaminal lumbar interbody fusion; PLIF, or posterior lumbar interbody fusion; and ALIF, or anterior lumbar interbody fusion.

The Class III other spondylolisthesis population was analyzed for effectiveness outcomes. The reports were stratified according to treatment with either posterolateral fusion with or without pedicle fixation, and compared to treatment with interbody procedures performed in combination with pedicle fixation. Conflicting data were noted regarding improvement in fusion rates and patient outcomes for patients treated with posterior procedures alone.

Notably, higher fusion rates and higher rates of successful clinical outcomes were noted for patients whose treatment included interbody fusion in combination with pedicle screw spinal systems.

A notable study analyzed in the course of this project was a

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systematic review by Kwon, which assessed the full treatment outcomes for 34 studies containing in excess of 1,000 subjects who were surgically treated for low-grade isthmic spondylolisthesis.

Important findings from this review were higher fusion rates were achieved with posterolateral fusion and pedicle fixation in comparison to non-instrumented fusion. The highest fusion rates were achieved with the combination of interbody fusion and pedicle fixation compared to posterolateral fusion with or without pedicle fixation. The fusion rates achieved using pedicle fixation for treatment of spondylolisthesis indications currently considered as Class III were comparable to or exceeded the 89% fusion rate in the historical cohort study.

In the Kwon study, higher rates of successful clinical outcomes were achieved with posterolateral fusion and pedicle fixation in comparison to non-instrumented fusion. In addition, higher rates of successful clinical outcomes were achieved with the combination of interbody fusion and pedicle fixation when compared to posterolateral fusion with or without pedicle screw instrumentation.

The clinical outcomes achieved using pedicle fixation for treatment of spondylolisthesis indications currently considered as Class III were comparable to the clinical outcomes reported in the historical cohort study. Recent literature provides a large body of data, which supports the use of pedicle screw spinal systems as an adjunct to fusion for treatment of

spondylolisthesis types currently considered as Class III.

In 2010, Sansur reviewed the database of the Scoliosis Research Society and assessed the records of 10,242 patients with adult isthmic and degenerative spondylolisthesis. Among the conclusions drawn from the Sansur study are: Surgical complications are proportional to the grade of spondylolisthesis. High-grade spondylolisthesis is associated with a higher rate of complication than low-grade spondylolisthesis. Degenerative spondylolisthesis is associated with a higher rate of complication than isthmic spondylolisthesis.

Notably, the types of spondylolisthesis with the highest complication rates are those considered as Class II indications for pedicle screw spinal system use. The Class III spondylolisthesis population, the group which is the subject of this Panel meeting, is associated with the lowest complication rates.

Data from the FDA targeted literature review also confirmed a favorable risk profile for use of pedicle screw spinal systems for treatment of spondylolisthesis types currently considered as Class III, in comparison to the spondylolisthesis patients reported in the historical cohort study.

Complication rates are less than 1% for a majority of events. Events with complication rates higher than 1% are shown.

FDA's conclusions based on review of the available literature regarding use of pedicle screw spinal systems as an adjunct to fusion for

treatment of spondylolisthesis types currently considered as Class III are that the available clinical evidence appears to support a reasonable assurance of safety and effectiveness.

The Panel will be requested to address the adequacy of the documented literature to support the use of pedicle screw spinal systems as an adjunct to fusion for treatment of spondylolisthesis types currently considered as Class III. The rationale for use of pedicle screw spinal systems in the treatment of DDD relates to the ability of rigid spinal instrumentation to limit strain during the process of fusion healing, thereby enhancing fusion success.

The previously identified literature relating to use of pedicle screw spinal systems as an adjunct to fusion in the treatment of degenerative disc disease was analyzed for effectiveness. This analysis included an assessment of fusion rates and patient outcomes and included a comparison to the historical cohort study.

Data exists to support higher posterolateral fusion rates with use of pedicle screw spinal systems compared to fusion without screws, although the existence of conflicting studies was noted. Higher fusion rates were achieved where pedicle screw spinal systems were used in combination with interbody fusion when compared to either posterolateral fusion using pedicle screws or when compared to non-instrumented posterolateral fusion. Fusion rates achieved with pedicle screw spinal systems for treatment of

degenerative disc disease were similar to or exceeded the 89% fusion rate reported in the historical cohort study.

Among the studies reviewed were results from two FDA-approved clinical trials. Regarding improvement in patient outcomes associated with the use of pedicle screw spinal systems for treatment of degenerative disc disease, conflicting reports regarding improvement in clinical outcomes with the use of pedicle screw spinal systems compared to non-instrumented fusion are acknowledged. However, multiple studies suggest that improved clinical outcomes are achieved with the use of pedicle screw spinal systems in conjunction with interbody fusion when compared to posterolateral fusion performed with or without pedicle fixation.

The lower rate of successful clinical outcomes with posterior procedures performed without interbody fusion has been attributed to persistent motion and nociception by inflammatory mediators at the level of the non-fused disc space.

The positive effect of interbody support on clinical outcomes for treatment of degenerative disc disease appears independent of whether the interbody fusion is performed through an ALIF, TLIF, or PLIF approach. The identified risks to health and overall complication rates were similar for treatment using pedicle screw spinal systems as an adjunct to fusion for DDD compared to existing Class II indications.

Data from the FDA targeted literature review demonstrated a

favorable risk profile regarding the use of pedicle screw spinal systems as an adjunct to fusion for treatment of degenerative disc disease in comparison to the historical cohort study. Minor differences were noted between these groups, but were not considered clinically meaningful. Lower rates for reoperation, revision, and removal were noted in the DDD population. A slightly higher rate of pseudarthrosis was noted in the DDD population, but was not considered clinically important due to multiple factors including the lack of a uniform definition of fusion across various studies.

The higher rate of implant breakage noted in the DDD population compared to the historical cohort study is attributed to the high percentage of patients treated with screw-plate systems in the cohort study compared to the Class III DDD population who were predominantly treated with screw-rod systems. It is suggested that this difference is related to the inherent mechanical properties of plate versus rod designs as screw-rod systems possess less resistance to bending over the instrumented spinal segments due to their lessened material condition compared to screw-plate systems.

FDA appreciates the limitations associated with the current medical literature related to spinal fusion for treatment of DDD, including lack of precise diagnostic criteria for degenerative disc disease, variable study methodologies, and a lack of the universally accepted definition for spinal fusion.

Despite these noted limitations, based on review of the literature regarding use of pedicle screw spinal systems as an adjunct to fusion for treatment of degenerative disc disease, FDA concludes that the clinical evidence appears to support a reasonable assurance of safety and effectiveness for pedicle screw spinal systems used in isolation or in combination with interbody fusion for treatment of degenerative disc disease.

The Panel will be requested to address the adequacy of the documented literature to support the use of pedicle screw spinal systems as an adjunct to fusion for treatment of DDD, which is currently considered Class III.

Thank you very much for your time and attention.

DR. KELLY: Thank you, Dr. Devlin.

Next we're going to hear from Dr. Ghambaryan regarding a systematic literature review.

DR. GHAMBARYAN: Good morning.

Today I will be presenting systematic literature review on use of pedicle screw instrumentation for fusion in degenerative disc disease patients.

The search of MEDLINE database identified 1,798 unique records: cadaver or non-human, case reports, non-systematic literature reviews, studies with sample size below 15, studies which did not contain

relevant outcomes, relevant device, or relevant study populations were excluded. Thirty-five studies assessing the safety and effectiveness of pedicle screw instrumentation including the use of autograft and allograft within a cage in DDD patients were reviewed.

Out of the 35 unique citations, 31 were primary status and 4 were secondary status. The follow-up in the primary investigations ranged from 6 to 96 months. In the primary research articles, the age ranged from 15 to 85. None of the authors reported that pedicle screw instrumentation was used in skeletally immature patients. Therefore, for the purpose of this review, all patients were considered skeletally mature.

The effectiveness of the pedicle screw instrumentation in the DDD patients was evaluated using fusion rate, which is the proportion of the patients from total sample who had successful fusion or union as reported by the investigators. The fusion rate was reported in 29 studies for a total of 3,108 patients. In addition, we included two studies with mixed patient population, which reported fusion rates separately for the DDD patients only.

The fusion rate ranges from 67 to 100%. The study with the fusion rate of 67 was conducted in 1993. DDD patients were a subgroup of only 14. Over 50% of the sample had prior surgeries, and semi-rigid pedicle screw plates were employed for fusion. The studies with large sample size reported fusion rate of 85 and 91%, respectively. The median fusion rate including Zedeblick's sub sample of the DDD patients was 94%.

The safety of the pedicle screw instrumentation was evaluated based on the reported adverse events during the surgery and postoperatively within 6 to 18 months. Thirty-one of the 32 primary research articles and one meta-analysis reported information on the adverse events. The most commonly reported adverse events were revision and reoperation, infection, and neurological complications. Revision and reoperation was reported in 17 studies and ranged from 0-37% with median revision of 9.4%. The main reasons for the revision and reoperation were pain and pseudarthrosis. Two articles in this review reported a rate of pedicle screw removal due to persistent pain above 20%.

Infection rate, which included superficial and deep wound infection and postoperative pneumonia was reported in 14 studies and ranged from 0-7%. Neurological complications were reported in certain studies and ranged from 0-14.8%. Investigation conducted by Audat in 2012 of 81 patients reported neurological complication rate of 14.8% for 12 patients. However, according to the authors, most of those complications were resolved with proper management and only foot drop persisted in three patients. Without taking into account this investigation, the range of neurological complications was 0-5.8%.

In summary, the fusion rate of pedicle screw instrumented fusion ranged from 67 to 100 with median of 94%. Most commonly reported adverse events were revision, reoperation, and neurological complications,

with pain and pseudarthrosis being the most common reason for surgery.

These conclusions, similarly to a previous review, are limited due to lack of uniformly accepted definition for degenerative disc disease, variable criteria used to define fusion success, variable definitions for reoperation, for example, elective removals versus adjacent level procedures. The heterogeneity of the patient population also contributed to the limitations of this finding due to patient's age, illness severity, surgical approach, number of levels requiring fusion, and constructs and grafts used for the pedicle screw instrumented fusion.

And now my colleague Stephanie Bechtold will provide regulatory and clinical overview for the dynamic stabilization.

MS. BECHTOLD: Thank you.

Good morning. My name is Stephanie Bechtold. I'm a biomedical engineer and scientific reviewer in the Anterior Spine Devices Branch in the Division of Orthopedic Devices.

I will now continue the discussion of pedicle screw spinal systems by introducing a subset of these systems called dynamic stabilization.

Thus far the scope of this discussion has been limited to the Class II and Class III indications for traditional rigid systems. These systems generally contain rigid, uniform, metallic rods. Clinical data is typically not required to support fusion indications, as the designs and clinical effectiveness of these systems are generally understood. However, more

recently a specific subgroup of pedicle screw spinal systems cleared under 510(k) with the same Class II and Class III indications as traditional rigid systems have been identified.

These have been termed dynamic stabilization systems, or DSS, since they contain semi-rigid, non-uniform, or non-metallic rods. Such features may include polymer cords, movable screw heads, or springs. 510(k) clearances were not supported with clinical data, and these systems were found substantially equivalent via mechanical testing, which was often modified from an established standard. These designs vary significantly from each other and from traditional rigid rod systems.

We will be asking the Panel what technological features fall under the scope of dynamic stabilization systems for fusion. Please note that today's discussion is restricted to fusion use of these dynamic stabilization systems. Non-fusion use is post-amendment Class III and falls outside the scope of this 515(i) discussion.

For the majority of the 510(k) cleared dynamic stabilization systems, only bench with or without some cadaver testing were used to establish equivalence. After clearance of these systems, FDA has received evidence from the clinical community to suggest that the bench testing conducted was not predictive of clinical outcomes. This evidence includes one recall of a device in this subgroup due to catastrophic device failures that were not predicted by the preclinical bench testing submitted in support of

510(k) clearance.

In order to assess the potential public health risks associated with these systems, we wanted to find out if dynamic stabilization systems were performing equivalently to traditional rigid systems in terms of fusion rate, device breakage rate, the need for secondary surgeries, and clinical failure modes.

To address the potential public health risk, FDA has the regulatory authority to order postmarket surveillance studies under Section 522 of the Act for any Class II or Class III device that meets any of the following criteria. Dynamic stabilization systems meet criteria 1 and 3 on this list: failure of the device would be reasonably likely to have a serious adverse health consequence, and the device is intended to be implanted in the body for more than one year.

Sixteen individual systems, each with multiple 510(k) clearances, were issued Section 522 postmarket surveillance orders in 2009 in order to gather evidence to address these public health questions. The current study status as of May 2013 is two studies are pending, four studies have inadequate progress, and 10 are on hold with a status of "other" meaning the sponsor is not marketing the product in the U.S. Of the six studies for devices that are being marketed, none are progressing adequately.

A systematic literature search was conducted in 2009 to support an issuance of the 522 orders. Several of these systems under 522

are also cleared with Class III indications and are subject to the 515(i) discussion today. Thus, the literature search was extended to the current day in order to gather additional information to assess whether sufficient evidence exists to address safety and effectiveness questions for these systems as an adjunct to fusion.

A majority of the literature available on these systems are for the non-fusion intended use, which is considered a Class III postmarket indication and is not subject to this 515(i). The predominant devices discussed include the Dynesys system and the Graf ligamentoplasty system, which is not marketed in the U.S., and hybrid constructs, which are used for fusion at one level and non-fusion at the adjacent level.

Several retrospective case series for the use of polymer PEEK rods for fusion are available. However, the patient numbers are small and the follow-up is short term, of less than 18 months. The authors recommend additional follow-up in order to fully assess these devices.

In summary, there is limited clinical evidence available to support the reasonable assurance of safety and effectiveness for dynamic stabilization systems when used as an adjunct to fusion for Class II and Class III indications. This is evident from the lack of progress in the 522 postmarket surveillance orders and in the limited number of studies and literature. These systems may present an unreasonable risk of illness or injury.

The Panel will be asked to discuss whether any risks to health

exist that are unique to the use of dynamic stabilization systems compared to traditional rigid systems.

Since there are several decades of clinical experience for pedicle screw spinal systems for both Class II and Class III indications, our Office of Surveillance and Biometrics, the product evaluation branch, conducted a search of FDA's Manufacture and User Facility Device Experience, or MAUDE, database to capture the types of adverse events reported.

Medical Device Reporting, or MDR, is the mechanism for FDA to receive significant medical device adverse events from manufacturers, importers, and user facilities. Information is gathered via the use of pre-specified patient or device problem codes, as well as a user narrative of the event. Multiple queries were created to identify all relevant MDRs from the MAUDE database. The searches were run by product code and date entered and were limited to reports received between January 1st, 2003, and December 31st, 2012. Over 6,000 unique MDRs were identified.

This table shows all patient and device problem codes with a greater than 1% proportion of adverse events within the product code grouping. The first row shows the total number of MDRs reported for each product code. Note that each MDR report can contain more than one patient or device problem code. The risks in the left-hand column are based on the device and patient problems codes associated with each MDR.

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Each subsequent column provides the number of patient and device problem codes by product code. NKB designates pedicle screws for Class III indications. MNH and MNI designate pedicle screws for Class II indications, and NQP designates dynamic stabilization. The corresponding proportion of adverse events is calculated as the incidence of each event out of the total number of reports for each product code. The total number of device uses under each product code is unknown.

Note that it appears that there is a large difference in the proportion of adverse events between Class II and Class III in the categories of additional procedures necessary and device removal.

To explain this issue, a text search was done on the NKB Class III MDR narratives. Terms such as "revision" and "removal" results in 38.6 and 43.6% proportions, respectively, which is more comparable to the reported proportion for the MNH/MNI Class II pedicle screws. This illustrates the inconsistencies in using end-user reported adverse event data.

Note also the higher proportion of serious adverse events such as device breakage, pain, and additional procedures necessary for the subgroup of dynamic stabilization systems under NQP. These differences could not be explained.

Because of several limitations associated with MAUDE searches, these results cannot stand on their own, but provide supplementary clinical evidence. Most importantly, because these systems are cleared for

multiple indications, the product code reported for an event may not correspond to the indication that was treated. In addition, as mentioned, a single MDR may be associated with more than one problem code.

Further, the lack of a device or a patient problem code in an MDR does not signify a specific adverse event did not occur. Thus, the true rates of incidence cannot be calculated. Problem codes were used verbatim instead of text searches to eliminate a potential source of bias. However, the problem codes may have been used incorrectly or inconsistently.

In conclusion, based upon the available clinical evidence, FDA believes that the safety and effectiveness profile for dynamic stabilization systems as an adjunct to fusion are not currently well understood. So, reasonable assurance of safety and effectiveness cannot be established. The subgroup of pedicle screw spinal systems may present an unreasonable risk of illness or injury.

However, in contrast, based upon the clinical evidence, FDA believes that there is a reasonable assurance of safety and effectiveness for traditional rigid pedicle screw spinal systems when used for DDD and types of spondylolisthesis other than severe spondylolisthesis or degenerative spondylolisthesis with objective evidence of neurologic impairment. We believe that the risks to health presented by these traditional rigid systems can be mitigated by the use of general and special controls.

I will now present the risks to health associated with pedicle

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screw spinal systems as well as the special controls used to mitigate these risks to health. Please note that since this Panel is preceding a proposed order in the Federal Register, this discussion of risks to health and special controls is being used to further formulate FDA's position, which will then be included in a future proposed order for public comment.

Since the 1993 and 1994 panel meetings, considerably more is known regarding the risk profile of pedicle screw spinal systems. Based on the clinical evidence shown here today, FDA considers the following list of risks to health to be associated with pedicle screw spinal systems. We would like to note that some of these risks might be applicable to general surgical procedures, such as cardiac, respiratory, or gastrointestinal, or might be applicable to other spinal instrumentation surgery for other indications, such as malpositioning, disassembly or breakage, and neurologic injury.

The Panel will be asked to discuss the completeness of this list of risks to health.

Based on the safety and effectiveness information provided in the responses to the 515(i) order, as well as information gathered by FDA and presented here today, FDA believes that for the remaining Class III indications for traditional, rigid, pedicle screw spinal systems, special controls can be developed to adequately mitigate the identified risks to health. Each of these special controls of labeling, biocompatibility, sterility, and mechanical testing is correlated to an identified risk to health. I will discuss these special

controls in detail in the following slides.

FDA often relies on national and international standards in order to provide guides and methods for characterizing medical devices. These standards can then be used across numerous manufacturers as a means for meaningful device comparison in 510(k) submissions for the purpose of establishing substantial equivalence.

The first proposed special control is labeling. Device labeling must bear all information required for the safe and effective use of the device. In addition to the labeling general controls associated for use with prescription devices, the labeling for pedicle screw spinal systems should include the following information: indications for use, including the levels of fixation; a clear description of technological features, including identification of device materials; device specific warnings, precautions, and indications; identification of MR compatibility status; sterilization and cleaning instructions; and detailed instructions of each surgical step.

In addition, some 515(i) respondents proposed elimination of the following warning from 888.3070 regarding the safety and effectiveness of pedicle screw spinal systems for Class II indication.

The Panel will be asked to comment on the adequacy of the labeling special controls and whether removal of the aforementioned warning is appropriate.

The second proposed special control is related to

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biocompatibility. Material characterization must demonstrate biocompatibility of the device materials and any potential byproducts, such as wear debris or leachates. Testing should be selected based on the identification of relevant patient contact type and duration using a method such as that suggested in ISO 10993.

In addition, characterization should include the identification of all relevant material standards to which each material in the system conforms. A full listing of the relevant material standards can be found in your panel package.

The third proposed special control is sterilization validation testing to mitigate the risk of infection. This control involves demonstrating the sterility of or the ability to sterilize the device components and any associated instruments with the sterility assurance level of 10^{-6} using a sterilization cycle that has been validated in accordance with the quality system regulation.

The final proposed special control is mechanical testing, which is heavily utilized as a special control for Class II orthopedic implants. Nonclinical performance testing must demonstrate the mechanical function and durability of the device components. Mechanical testing should include static and fatigue testing of the construct and/or subassembly.

Note that depending on the technological characteristics of the device and/or the modifications being made, FDA may also request additional

mechanical testing not necessarily outlined here, such as shear testing, disassociation testing, or wear characterization, in order to determine substantial equivalence.

Construct testing using a method such as that suggested in ASTM F1717 can be used to compare device performance in a worst-case vertebrectomy model. The standard outlines methods for static and dynamic compression bending, as well as static torsion and tension bending. FDA's spinal system 510(k) document recommends static and dynamic compression bending and static torsion testing for posterior non-cervical pedicle screw spinal systems.

Note that for dynamic stabilization systems, this testing is often modified from what is prescribed in the standard due to different technological characteristics. Thus, it is unclear if this special control is adequate to mitigate the risks associated with this subgroup of systems.

Subassembly testing using methods such as those suggested in ASTM F1798 can be used to evaluate the inner connection mechanisms between components such as screws and rods or hooks and rods. FDA considers mechanical testing per ASTM F1798 to be useful for evaluating individual components in spinal systems, especially in cases where modifications are being proposed to the components that affect inter connection mechanisms.

FDA correlates the ability of each of these of special controls to

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mitigate and identify risks to health. Based on the responses to the 515(i) order and the clinical evidence gathered, the special controls are considered adequate to mitigate each risk to health associated with pedicle screw spinal systems. As shown on this first table, all areas of controls can be used to mitigate the risks to health.

It is noted that we disagree that implant loosening such as loosening at the bone implant interface is directly addressed through mechanical testing. However, we believe the current body of clinical evidence shows that the other proposed special controls mitigate the risk of implant loosening.

This slide continues the list of risks to health and associated special controls. Labeling is the predominant special control for the mitigation of these risks.

In summary, based on the available clinical evidence, the following special controls are suggested for pedicle screw spinal systems: labeling, biocompatibility, sterilization, and mechanical testing, in addition to any other special controls identified by the Panel.

The Panel will be asked to comment on the adequacy of the proposed special controls to mitigate the risks to health for traditional rigid pedicle screw spinal systems and dynamic stabilization systems used as an adjunct to fusion.

And, now, a final summary of the safety and effectiveness for

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pedicle screw spinal systems. Due to the small amount of published literature and clinical evidence available on these devices, FDA believes that the safety and effectiveness profile for dynamic stabilization systems when used as an adjunct to fusion is not well established, and the risks are not well characterized, and special controls utilized for traditional rigid systems may not be appropriate to mitigate the risks to health for dynamic stabilization.

Based upon clinically observed failures, the nonclinical testing identified for traditional systems may not be sufficient. These systems may present an unreasonable risk of illness or injury. However, in contrast, based on the clinical evidence presented, a reasonable assurance of safety and effectiveness may be shown for traditional rigid pedicle screw systems for Class III indications. Furthermore, the proposed special controls are sufficient, and there is an absence of unreasonable risk of illness or injury for the traditional rigid pedicle screw spinal systems when general and special controls are applied.

We would like to thank the Panel for their time and attention, and we are available for any questions.

DR. KELLY: I'd like to thank all the FDA speakers for their presentations. And at this point I'd like to ask the Panel if they have any brief clarifying questions for the FDA speakers. And please remember, this Panel may also be questioned during our deliberations session later this afternoon. The Panel has any questions for our presenters?

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I see Dr. Lyman first.

DR. LYMAN: Yes. With the summary of literature, I didn't have any sense at all of what timeframe was being used in these studies to define these outcomes of these events. And so, that makes a big difference if you're talking about infection or fracture or revision surgery, if you're looking at six weeks or six months or six years. And none of that was in the presentation. Can anybody comment on the length of follow-up for these studies and whether or not that's comparable between the different groups that are being compared? Thank you.

DR. GHAMBARYAN: If you're referring to --

DR. KELLY: If you'd come to the microphone and announce your name, please? Thank you.

DR. GHAMBARYAN: Anna Ghambaryan. If you're referring to --

DR. KELLY: Remember, please announce your name for the transcriptionist and for the benefit of our panel. Thank you.

DR. GHAMBARYAN: It's Anna Ghambaryan. If you're referring to the systematic literature review, the adverse events were captured in the timeframe of 6 to 18 months, but the systematic literature review was done for only DDD patients. If you have questions to the targeted literature review, then Dr. Devlin should answer those.

DR. DEVLIN: Dr. Vincent Devlin.

DR. KELLY: You got to press the button --

DR. DEVLIN: Dr. Vincent Devlin.

In the target literature review, follow-up less than 12 months was excluded, so all the studies had an excess of 12 months follow-up.

DR. KELLY: Sure.

DR. LYMAN: Just following up on that, so do you have any sense of when you're comparing one to another to another, whether or not the lengths of follow-up were equivalent? Because if we're looking at 40% versus 30%, that could be completely explained by length of follow-up, you know. So I just -- I needed clarification of that.

DR. DEVLIN: The literature is very variable, so it's not possible to make those fine distinctions because of the poor quality of the literature.

DR. GHAMBARYAN: I would concur.

DR. KELLY: Dr. Potter has a question.

DR. POTTER: A quick question for Dr. Ghambaryan. In your assessment of effectiveness of fusion rate, do you have a sense of what percentage of the studies used cross-sectional imaging, i.e., CT or MR, to assess fusion as opposed to plain radiographs?

DR. GHAMBARYAN: No. We included studies from 1990 to 2012 and -- 2013 actually. And in some of the studies they would just report that patients had fusion, in some of the studies they would say it was radiographically confirmed, and in other studies they would describe the protocol which they used at what time period to confirm the fusion. And we

used that as our limitation because we had to rely on others.

DR. KELLY: Mr. O'Brien?

MR. O'BRIEN: Yes. Joe O'Brien.

Dr. Devlin had indicated in his safety presentation the -- he noted the difference in the outcomes on breakage for screw-plate versus screw-rod outcomes, which just brings a basic question I had that -- as noted by Dr. Kavlock, and as I looked through the literature, the early FDA terminology was specifically pedicle fixation, and at some point it evolved to include spinal system. And I was just curious.

Was that just an evolution, or was there actually a specific panel or a certain terminal point where it was extended from fixation, pedicle fixation to pedicle spine system?

DR. DEVLIN: I would defer to one of my regulatory colleagues. I believe that would be due to more sophistication in engineering definitions.

DR. KELLY: Anyone have a comment from the FDA?

DR. JEAN: Hi. Ronald Jean.

I believe your question is just asking about the terminology that we used. And, again, in terms of description, we outlined the regulatory history of pedicle fixation systems. They became classified as pedicle screw spinal systems, and then anything within that classification bucket that is found substantially equivalent becomes incorporated. So in terms of the terminology, our official recognized terminology is pedicle screw spinal

system. It does incorporate rod-screw systems as well as plate-screw systems. Does that satisfy --

MR. O'BRIEN: Well, it does. Just to be honest, it became very difficult to assess what we're being asked to assess because it now includes the entitled spine system. So when I look for a -- if I look at the dynamic stabilization system, it may be a fixed screw anchor with a different polymer or some other type material broad or longitudinal connection. So to me that would be a fixation. There's a difference between a pedicle fixation versus the structure -- the system, so -- yet we're being asked to look at the spine system when we look at rigid, you know. So it just begs the question to me as to what I'm really looking at and asked to approve, you know.

DR. JEAN: Sure.

MR. O'BRIEN: I have no problem with fixation system, but if you include it with other things, then that becomes a little bit more complex.

DR. JEAN: Sure. And we did our best to lay out what we are asking the Panel to deliberate on. But to clearly break it out, we are asking you to weigh in on traditional rigid pedicle screw systems. The system as a whole for use for DDD, secondly for use with the other types of spondylolisthesis that are currently Class III, and then in terms of dynamic stabilization we are asking you to deliberate as a whole on that class of products.

MR. O'BRIEN: Okay. Thank you.

DR. KELLY: Dr. Do.

DR. DO: Yes, I got a little confused. We're not -- you presented data on degenerative disc disease, DDD, as Class III. So are those just degenerative disc disease without any spondylolisthesis whatsoever? But we're not being asked to give our recommendation for those Class III systems to downgrade them to Class II. Is that correct?

DR. DEVLIN: I'm sorry. I'm not understanding that question.

DR. DO: So the data presented treatment -- using pedicle screws for Class III DDD. And what is a Class III DDD?

DR. DEVLIN: Any degenerative disc disease would be classified as DDD under the current system. Spondylolisthesis as a consequence of how it was approved or cleared back in the time of the 1994 panel meeting had specific limitations on the types of spondylolisthesis. The ones that were not cleared were labeled "other."

DR. KELLY: Dr. Do, it's they're Class III devices, not a Class III DDD.

DR. DO: No, no, I know. But the -- I got confused because we're asked to give our opinion on non-degenerative spondylolisthesis grade 1 and 2. But the data that was presented included the degenerative disc disease where the device was classified as Class III.

DR. KELLY: The two cohorts we're asked to comment upon, DDD and the other spondylos, less severe ones, so the two questions of really

two indications are being asked for us to consider. Mr. Melkerson may help us.

MR. MELKERSON: Don't know if this will help -- don't know if this helps or hinders, but many of the definitions of degenerative disc disease included up to grade 1 spondylolisthesis. So when you're looking at other spondy, we're trying to capture all other spondys other than degenerative because the --

DR. KELLY: And that leads me to the question that's probably why we're asked to clarify the definition of DDD.

MR. MELKERSON: That is correct.

DR. KELLY: Any other -- yes, Bernard.

DR. PFEIFER: Dr. Pfeifer.

As I tell my kids the laws of ancient medicine, I was around at the evolution of these things when they started. To answer Mr. O'Brien's question, the initial systems as I recall were plate and screw systems, and then evolved into the rod systems with multi-points with all the other things that we have today. The historical cohort study probably -- and in my recollection did include both systems, but the nomenclature changed over time. And I think it's a nomenclature issue as opposed to a change -- a significant change in product. Maybe that's a way of putting it? So if that helps --

DR. KELLY: Any other questions for the FDA Panel?

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Very well. I'd like to thank all the FDA speakers for their diligence and their preparation.

I think at this point, if it's okay with Mr. Melkerson, we could proceed to the deliberations around the FDA questions. I want to open the floor to the experts around the table.

Let's have a consensus. Who wants a short break, or would you rather continue? I think we're going to continue.

Oh, I see. Okay. Not all the public -- all right. All right. So we're going to jump start -- jump skip. Since not all of our public speakers are here, we'll go the Panel deliberations structure on the FDA questions.

I will open the floor to the experts around the table to begin deliberating on any issues you may have with any data you've heard today, either this morning or the material you've read prior to your arrival.

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

During the next hour we'll open the floor to questions to the FDA. Is the FDA prepared to respond to further questions posed this morning? We just obviously heard that we're not.

I have no further questions so I'd like to begin the deliberations. Panel members, we should discuss what you're heard this

morning in relation to the questions we're asked to answer. And, again, you can have the opportunity to ask the FDA any questions at this time. And, again, if the FDA is going to respond, I ask them to come back to the microphone and identify themselves for the record.

I'd like to stress it's important to hear from all of you. You're here for a reason. You all have different skill sets and backgrounds and talents, so I'd like to begin deliberations, questions, and comments on what we heard this morning.

Yes, Dr. Lyman?

DR. LYMAN: Stephen Lyman.

I just had a question for the clinical colleagues here on the Panel because I'm an epidemiologist. I do this sort of research, but not necessarily in spine, so if we can clarify a few points just to help me understand what we've seen today.

One question is whether or not hardware removal is elective or if that's being done to treat other symptoms that the patient's having? I know in other procedures you may remove hardware after fusion has occurred, so that's one question.

Another is, if you have non-fusion, does everyone go back to surgery, or what are the treatment options at that point? Is that completely a failure, or is that sort of a gray area based on surgeon choice and patient choice?

And just a point of clarification on terminology. Are these considered instrumented fusions? I've read that phrase in the literature. I'm just not sure whether or not that is what this is or if that's actually referring to something else. Thank you.

DR. KELLY: Dr. Lehman and then Dr. Graf can tackle those questions.

DR. LEHMAN: Hi. Ron Lehman.

I guess I'll go in reverse order. So instrumented fusion is correct, or anything with implants implanted into the spine, so as a generic panacea. The previous question about fusions, just because someone does not fuse does not mean they need another operation. Similar to when someone goes to surgery because someone has an abnormal MRI, they shouldn't get a surgery for an abnormal MRI. So if they have symptoms, they get a surgery.

And the same thing, if someone -- you know, I think most of the studies have shown that for a one-level posterolateral fusion, I mean obviously the numbers are all over the place, but 83 to 87% chance of fusion at one year by radiographic evidence, not necessarily cross-sectional imaging, but by radiographs once again reported by the surgeons, the authors. But even if you don't fuse, it does not mean you'll need another surgery. So if you're asymptomatic, it doesn't necessarily mean another surgery unless something else is going on.

And the first question -- refresh me again, I'm sorry.

DR. LYMAN: Sorry. That was whether or not removal was elective?

DR. LEHMAN: Yeah, I mean that's certainly once again based upon patient symptoms. Sometimes it's elective. There are some surgeons I think who take out screw instrumentation if someone fuses, but I think that's far in the minority. Typically when implants are removed, it's because the patient is having symptoms, whether it be radiculopathy, infection, or they had pseudarthrosis, failure to fuse, and they need another operation from that standpoint.

DR. LYMAN: Okay. Thank you. I think my concern is we're looking at -- you know, these are systems, but they're being used with a lot of different approaches. And teasing out the approach -- the complication is the result of the approach versus the choice of system. And then you have -- we're focusing on these pedicle screw systems, but then there are other hardware associated with that, and that hardware may change. So it seems almost impossible to tease out from at least the literature we've seen today what's causing what. Is it the system? Is it the approach? Is it the additional hardware? Is that a fair assessment?

DR. KELLY: From my meager understanding of spine surgery, I think that is fair, Steve.

Did you want to comment, Dr. Graf? And then we'll hear from

Dr. Pfeifer?

DR. GRAF: No. Dr. Lehman really covered your topics. As far as hardware removal, for the most part it's not a scheduled or elective thing. It's based upon patient symptoms. There are some more minimally invasive spinal systems which are used for fractures, which instrument a larger number of levels, which are then removed to -- for younger patients and whatnot to reduce the number of levels that are fused once a fracture is healed. Again, as Ronald touched on, asymptomatic pseudarthrosis, they don't have to be removed. It's based upon patient symptoms, again. And you're right about the instrumented fusion.

DR. KELLY: And I want to propose just a thought question just to get some spirit of protecting our patients. To me, as a shoulder sports surgeon, my understanding, my meager understanding is that the indications for DDD spinal fusion are still kind of murky. And just I'm trying to protect that patient out in the middle of nowhere.

Will this declassification promote more fusions perhaps? I know this is maybe not our charge today, but I think that question has to be posed to the Panel with the patient in mind. Are the indications to the spine surgeons particularly here today, are they still questionable? And do you think that declassifying this will promote the performance of unnecessary fusions?

Dr. Graf?

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DR. GRAF: I don't necessarily think that the change in this classification will change anybody's practice because this is done regardless on a daily basis around the country. And it's really based upon the surgeon, how aggressive the surgeon is in treating this certain pathology. I don't think that that will -- that this will encourage or discourage in any way a particular surgeon's preference as to how to treat a certain spinal pathology. I don't think it'll promote more fusions for degenerative disc disease.

DR. KELLY: I haven't heard from Dr. Rohr in a bit. Dr. Rohr, you want to weigh in?

DR. ROHR: Yeah, my question is -- I guess it will involve mostly the FDA. We're also being asked to discuss dynamic stabilization systems. How do you differentiate -- I mean all rods -- the Harrington rods we used to use are certainly more flexible than the systems today, and yet they were considered a rigid system. What is the differentiation between a rigid and a dynamic system? How are you differentiating those so that we know which ones we're talking about is question one?

MR. MELKERSON: I was going to say that's part of the reason why we're in the situation we're in is there is a range of flexibility both in metallic, polymer, and other design features where the screw connections were allowed to slide or move, other things that were using polymer bands. So the question that we were having is they were found equivalent to the systems using some modification of testing. Can you help us try to just tease

those out? Because we're wrestling with that same question. That's why the question's there.

DR. ROHR: It's a difficult question, especially considering historical systems.

The second part is, how many systems are actually marketed, sold, cleared, or approved in the United States that are considered dynamic or flexible systems? I mean they're actually on the market that the manufacturer promotes that aspect of them?

MS. BECHTOLD: Stephanie Bechtold.

At the initial time of the issuance of the Section 522 orders, we identified 16 unique systems that fell into the criteria that Mr. Melkerson described, varying screw positioning, different materials for the longitudinal elements, for example. Out of those 16, I believe 6 are currently being marketed in the U.S. The rest have all put their marketing plans on hold and are not actively marketing.

DR. KELLY: Perhaps a clarification would be more appropriate to label them as semi-rigid versus dynamic, and it's a big distinction. If the materials have some leeway versus something that's designed to move, I think that's probably an important distinction.

Dr. Golish, do you want to weigh in on this? You have a mechanic background.

DR. GOLISH: Yeah, I have a direct comment on that. So in the

FDA presentation on dynamic stabilization -- and that is a historical and possibly unfortunate term -- it was suggested that these devices may represent an unreasonable risk, which on our flowchart puts them rather quickly into the Class III before we go very far through the flowchart.

There's another possibility I think that Mr. Melkerson perhaps is suggesting and Dr. Rohr was commenting on is that it is possible, I think at least conceivable, to develop some special controls that distinguish the dynamic or semi-rigid devices from rigid devices, regardless of whether the Panel thinks they're an unreasonable risk. And so, I think further down the classification flowchart, the possibility of special controls to subset rigid versus dynamic or semi-rigid is at least possible. So we ought to consider that irrespective of whether we think there's an unreasonable risk or not.

DR. KELLY: I just want to hear from Dr. Lehman, and then we'll go to Pfeifer and O'Brien.

Dr. Lehman?

DR. LEHMAN: Hi. Ron Lehman.

And another thing actually to answer Mr. O'Brien's question he posed a little while ago, as well as Dr. Golish, but, you know, I think even when we look at these "dynamic stabilization systems" as outlined, one of the things the tenets in the document said moveable heads. So when we look at pedicle screw fixation there are multiple types of screw shaft to screw head or tulip type connections, one is fixed where there's no movement

whatsoever, one is a unilateral screw where it moves just in one plane, and the other ones are multi or polyaxial heads.

So although technically these move and these are dynamic, once you place a set screw and lock it into a rod, it becomes a rigid system. I think the clarification with rigid versus dynamic stabilization should be more in the connection between the screws, so if we look at more rigid types of fixation, we look at titanium rods versus chrome rods versus stainless rods with set screw application. They're meant to be rigid or fixed in place and not have any immediate stability concerns, if the patient fuses all that type of stuff, versus dynamic type systems.

Or it can be polymer connections, sheath connections, soft tissue connections in between the two pedicle type screws. As Mr. O'Brien pointed out before, we place pedicle screws into the vertebral body through the pedicle hopefully with good placement. The connection then between those two screws, if you're looking at say L3-4, the pedicle screw is a fixed type of device. And then the connection, though, as some of these devices have espoused more for a fusion-less technology, I think, even than fusion-enhanced or promoted technology, is a little bit different.

And so, I think if we look at it from that standpoint, constructs or screw systems that are intended to provide immediate stability are different from ones that are intended to allow for a dynamization or movement immediately, if that makes sense.

DR. KELLY: I think so.

Dr. Pfeifer? And then -- Mr. O'Brien.

DR. PFEIFER: Several comments. I beg your indulgence.

Dr. Pfeifer.

What you just described, Dr. Lehman, is still a rigid system. It has a moveable screw for placement, but then once you connect it, it becomes a rigid system. And that is not to be compared to the semi-rigid system in Dr. Zdeblick's study, which was quoted, where essentially you had a hook system into the screw that was completely moveable. And even though it's called semi-rigid, it probably was non-rigid, which is why the rates looked the same.

The issue of dynamic stabilization is how strong a construct do you want? Do you want a construct that's going to give you a fusion right now at the level you're dealing with? And the benefit is the more rigid, the more construct it gives you, but since all discs are made by the same manufacturer -- I'm talking about the natural discs that came there -- and subjected to the same forces, it now stresses the disc at the level above or below and transfers force. And the thought is that that is going to make that disc "wear out" sooner.

And so, introducing a system that allows the construct -- and there we talk about bone prosthesis or bone, excuse me, screw system, some "mobility" -- in other words less rigidity -- theoretically should transfer less

force and make the next level or the adjacent levels wear out sooner [sic].

We're learning about this. And taken to the extreme is the European systems that have no fusion at all, but just stabilize one system.

Now, the other comment I have is we have to be a little bit careful about degenerative disc disease, which to the surgeon or to me seems to say there's no slip, there's no spondy. It's just a degenerative disc versus the degenerative grade 1 and 2 spondylolisthesis, which is the Class III classification we're talking about in the systems here.

And then, finally, a question on the MAUDE database. First of all, we don't have the n of the number of systems that have been implanted, so this is only a relative comparison of the system indication. It is not an absolute 37% fracture rate of hardware of all the implants put in. The fracture rate is probably much lower than that, if you knew the n .

But my question on hardware removal is hardware removal is done -- for revision of surgery, sometimes done because the level above got in trouble and you're going to remove the original implant. And is that a reportable event under the MAUDE database, or is this only considered an event of removal for problems with that hardware itself? In other words, are the manufacturers required to report -- the rep comes in, you took out a one-level fixation, put in a two-level fixation because now the disease has spread to the level above, is that a reportable event under the MAUDE database? Can anybody answer that question for me?

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DR. JEAN: Hi. Ronald Jean.

In terms of the question about the MAUDE database, the events are as reported, so sometimes it could be at the original index level, sometimes it could be something that is adjacent. We do recognize there are limitations to the data that we collect through the MAUDE database as well as the literature that you're currently evaluating.

But I did want to add a comment, if I may about dynamic stabilization. So the 16 systems that we had described in our presentation that were originally cleared, we had termed them as falling within this bucket of dynamic stabilization. Some of them had the dynamization feature within the longitudinal member, some designs actually have that slightly incorporated within the screw design, and what we are saying and what we are asking you to evaluate is whether there is a reasonable assurance of safety and effectiveness for that class of products.

And although we originally cleared those products through 510(k), they were cleared based on bench testing. And subsequently we identified safety signals, issued the 522 orders, and we are still at a point where we do not have a lot of information on those systems. So we are asking you first to consider the classification question, but also to help us identify what would you consider as constituting a dynamic stabilization system? And, perhaps, are there any systems that we identified as belonging to that bucket that maybe are more in line with the traditional rigid fixation?

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DR. PFEIFER: But, if I may, they are still cleared only as an adjunct to fusion. They are not cleared as a standalone device?

DR. JEAN: Correct. We are purely talking about systems as an adjunct to fusion here. If it is intended for non-fusion use, as was discussed for the Zimmer Dynesys a couple of years back at the Panel, that would be Class III PMA.

DR. KELLY: I think Dr. Pfeifer brings up many good points, one of which is terminology. And if there may be some salubrious or helpful effect of a little motion in potentiating fusion like we see with titanium versus stainless steel, and/or if it prevents adjacent segment disease, I think we have to really debate the terminology here. What is truly dynamic versus what is otherwise?

Mr. O'Brien?

MR. O'BRIEN: Just to follow up on a couple things. First, you know, as Dr Pfeifer brings up with adjacent segment disease, yet that's not listed as one of the potential risks on the list here, and should that be added as one of the potential risks that we look at for this --

DR. KELLY: That's one of our questions, so I'm glad you brought that up, so we'll debate that.

MR. O'BRIEN: I would suggest it is.

Secondly, to get back to your question that you posed about the downing of the classification is that going to increase fusion, and what

does that do from a patient perspective. You know, as Dr. Graf had said, it's likely that an individual practitioner may not change his practice. But I think history would probably show us that indeed if you down-classified, there will probably be an increase of both instrumentation and fusions that occur as a natural response to that.

From a patient perspective, I mean clearly that's one of the things that I look at from a patient perspective and as a patient. However, I would address that to say that for the most part patients -- outside of true safety issues, you know, patients are not so worried about what it is that's used. And to that extent, as a patient I want to make sure that the provider has all of the tools in their toolbox that they need to provide the best care.

The patient's journey isn't so much about instrumented versus non-instrumented, pedicle screw versus hook, or plate versus rod, necessarily. What they're looking at is their activities of daily living, their pain, their symptoms, et cetera. And the journey is often very complicated because you may have at first a non-operative treatment that isn't successful. You may then have a non-instrumented treatment that isn't successful. And then you have an instrumented treatment that may or may not work in 70% of the time, so it's a very frustrating, costly, and painful journey that's there.

So the fundamental issue isn't really one versus the other. So the question becomes what's difficult because that's not under the FDA purview in terms of diagnosis and all of those things which really impact the

patient --

DR. KELLY: I agree with you. We're not ethicists here. It's just that, again, this is the outsider's sports shoulder opinion that the last Cochrane Review I was apprised of showed if you look at DDD, it's non-operative treatment versus fusion, there was no material difference. So maybe -- what I'm posing is maybe without the special control, that they failed this, this, and this, and therefore -- I'm just trying to safeguard the abuse of this technology when the indications to me -- and maybe Dr. Haines can weigh in -- are still rather nebulous.

MR. O'BRIEN: They are nebulous. But I guess I was just trying to say at the end of the day to -- it's almost like gun control, you know. You can have a safe gun, but if it's in the wrong hands --

DR. KELLY: As we say in Boston, Joe, don't get me started about that.

MR. O'BRIEN: No, but if it's in the wrong hands and used at the wrong time for the wrong purpose, then it's not good. But it could be a very safe gun so, you know.

DR. KELLY: I would beg to differ, but anyway --

MR. O'BRIEN: I see it the same as pedicle screws.

DR. KELLY: Dr. Haines, do you want to weigh in on this?

DR. HAINES: Yeah, I think Mr. O'Brien helps to clarify -- we're on the edge here between whether we're dealing with a tool or with a

treatment. And we've -- I think I understand historically how we got into the business of talking about what the uses -- what the medical indications are and how physicians should use these devices. But we've ended up at this stage in a very unusual situation where, in spondylolisthesis, the indications for the most difficult operations with the greatest risk are Class II and with the least risk are Class III. And that's an absurd place to be.

And I think the DDD discussion is dangerously close to regulating medical practice instead of thinking about the safety and effectiveness of the tool. And my own interpretation of this is that we've reached the point where we've gotten mass amounts of data that suggest that pedicle -- that rigid fixation systems work and if they're placed with expertise have reasonable safety and that we really shouldn't be parsing the little differences in indications for use and so on. That's beyond the scope of what can reasonably be done through regulation, and it merges into the practice of medicine.

DR. KELLY: I agree with you wholeheartedly. It's just you're protecting patient care though. I think that maybe it would be reasonable just to inject, you know, caution, controls, and so forth. I'm just concerned about the abuse of the technology.

DR. HAINES: Oh, yes we are.

DR. KELLY: I mean I'm saying that having practiced in Philadelphia for 23 years.

Dr. Lyman, you had a comment?

DR. LYMAN: Just along those lines, I'm not convinced that we necessarily do have a lot of information showing that these systems work based on what we saw today, and I think that's one of my concerns. There's nothing in the FDA's suggestions for controls as any sort of postmarketing surveillance. There's no clinical data that's going to be applied to these questions. And I think that's really where the burning questions remain-- are these safe and effective devices with really high-quality studies?

And I think we're on the cusp of being able to do that very efficiently with the advent of ICD-10 and some of the other processes that are under way in improving the quality of the data that we have just being captured through standard clinical care.

DR. KELLY: Dr. Jean, you have a clarifying comment?

DR. JEAN: Sure. I just wanted to clarify the point that you raised about comparing this to conservative care. I just want to make it clear for the record that we are not talking about comparative effectiveness at this Panel meeting. What we are asking you is first to help us refine the definition of DDD as best as you can. And Dr. Haines did make an astute comment that some of this falls within the realm of the practice of medicine.

The second thing I want to point out is based on your charge to actually consider the intended -- the indication for use of DDD, we have very clear regulatory classification procedures. So that is what you're being asked

to consider for the DDD indication for use. And to help you get a gauge of where the pedicle screws stand for other uses, we've laid out the landscape of all of the other Class II indications for use so you can compare against some of the outcomes there. Thank you.

DR. KELLY: Thank you.

Dr. Golish?

DR. GOLISH: Yeah, I have an immediate follow-up on that point, Dr. Haines' point and Dr. Pfeifer's point about DDD, is that this is an extremely complex issue that has gone on for decades for a couple of related reasons. One reason is that it's a complex clinicopathologic entity, the definition and understanding of which has evolved over time. Another reason is that the interaction among sponsors and the FDA has served to conflate the definition even further as it's shrunk and enlarged including other adjacent clinicopathologic entities.

So I have a modest proposal, which is that we define a necessary -- not necessarily sufficient, but a necessary condition for DDD, radiographically at least. MR signal changes, loss of height, I think most people would agree on those things as necessary elements, and other elements may or may not be included depending on the situation, as they have been over many years of IDE trials that some of us here have debated in the relatively recent past.

DR. KELLY: Dr. Pfeifer is shaking his head. I want to hear

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Dr. Pfeifer's rebuttal.

DR. PFEIFER: Well, again, I'm not a fan of the argument, but there are people who would argue that the more open the disc space is, the more symptomatic it is, and as it starts to narrow, it becomes asymptomatic. So, again, these are arguments that we spent -- at least the New England Spine Study Group spent a whole day on a beautiful ski day up at Loon Mountain sitting inside talking about it, not coming to a solution, and various other panels have. The best thing that we have right now is what Dave Fardon published with the North American Spine Society's nomenclature description, and that's the best I got. I'll listen to somebody else.

DR. KELLY: Quickly, Ray, off that?

DR. GOLISH: I agree with your sentiment there. And we may make a small useful contribution to this debate today, and we might also choose to debate it all day and conclude very little. So I agree with the idea of a modest proposal.

DR. KELLY: Dr. Lehman had his hand up first, I think.

DR. LEHMAN: Yeah, I think I certainly agree with all these things. I mean I think the issue of DDD is very -- it's very taxing. I think we could have this Panel for the next 3½ months meet every day till long into the night, and it would still be very difficult I think to come to a complete consensus.

As far as if people are going to use these devices more if the issuance of DDD is incorporated into a potential Class II, I think I would posit that surgeons -- you know, regardless of how they treat patients, hopefully there's a large amount of non-surgical care, all that type of stuff. When they deem that they have to do something in terms of intervention, they're going to use something. And so, if it's, you know, grade 3 and 4 spondylolisthesis in the past, uninstrumented posterolateral fusion has been the standard of care for 40+ years.

Now, if a patient would come to me after having a surgery of posterolateral fusion for a grade 3 or 4 spondylolisthesis without implants, I'd be very surprised. I'm almost to the point now where I would say it's essentially standard of care. Most posterolateral fusions performed as well, whether it's TLIF, PLIF, standard posterolateral fusions, they come without pedicle screw instrumentation or implants, I would be surprised.

Hook constructs, wire constructs in the lumbar spine, we know from a 2003 article there's a significant amount of canal intrusion that occurs. Up to 30% of -- even a pediatric placed pedicle hook will intrude the spinal canal by 30%. Even a well-placed pedicle screw in theory should be less than 6 mm, which is less than that. So I think things have certainly changed now even from the early 1990s where these things are now being used by the large or vast majority of spine surgeons from that perspective.

The other issue with adjacent segment degeneration, I think, is

a very unique and interesting topic. I do a lot of cervical arthroplasty. There's been a lot of information and literature about lumbar and cervical arthroplasty, which is certainly much different than fusion devices. And one of the things these have been espoused to do is to decrease the risk of adjacent segment degeneration. What we've found now with seven-year prospective randomized trials with IDE data from several of the initial IDE studies is that that has been not to be the case.

Although discs do degenerate above and below constructs with the re-fusion or arthroplasty constructs, there's more data currently in the last 2½ years that suggest that it may be genetic in nature. The one true thing we found out from the arthroplasty studies is that the less of an operation tends to be less at the index level with arthroplasties versus fusion, at least in the cervical spine. So once again, it does occur. Is it genetic? Is it because of the surgery?

Certainly the 1999 Hilibrand article where we looked at -- or where they found a 2.9% instance of radiographic adjacent segment degeneration probably has been significantly affected, and is there a different thought within just the last, you know, two to three years. So all these things I think are ongoing and, you know, certainly open to discussion.

DR. KELLY: Actually, Dr. Potter, yes?

DR. POTTER: Just a -- Hollis Potter. Just a comment on the radiographic assessment of disc degeneration, or DDD. I concur with

Dr. Haines. I can give you a whole bunch of radiographic definitions, and I'm sure Dr. Do can as well, ranging from looking at pure radiographs of disc space narrowing, endplate changes, to MR. We can go the gamut from literally modic changes at the endplates to the 5-point Fuhrman classification that looks at multiple variables on MR. And even from a biochemical standpoint, we can use MR metrics such as T1 rho to assess proteoglycan depletion in the disc, but these are not ubiquitous. These are largely -- the latter is largely research-based technique.

At the end of the day, the surgeons around the Panel are treating patients, not MRs. So my sense is for the FDA to constrain use of these devices that have been out and have been shown in my experience efficacious for a long period of time, about some sort of constraining definition of degenerative disc disease, including a specific radiographic one, is not appropriate.

DR. KELLY: Especially since, you know -- we know the correlation of -- defining symptoms is really weak. So I just want to make that comment I made earlier. We're not here to serve as ethicists, but I'm just thinking of that little old man that may be preyed upon.

So I think that we have a few more minutes for questions to the FDA; then we can maybe take a break and do our open public hearing. Is there any other questions for the FDA?

Dr. Do?

DR. DO: Yes, Huy Do.

I'm still confused. It's still a question for the FDA.

DR. KELLY: That's my baseline. Don't worry.

DR. DO: Two questions. One is the MAUDE database. As I understand it these are voluntary reporting. So do you have any idea that what's the ratio of -- are they inclusive? How inclusive are they from the reporting standpoint in terms of adverse events?

And number two is, you've asked us to sort of better define DDD into something like degenerative spinal pathology. My question is what would you use that for? Is that going to help you with the medical literature review? I still am unclear as to what our recommendation would be used for.

MR. MELKERSON: I'll try to handle the first one. The MAUDE database is just that. It's a voluntary reporting, so you have numerical -- or numerator information, but no denominator information. So what percentage of what it represent -- it's useful in identifying the types of adverse events, but not necessarily the occurrence rates. But if we do see a large uptick in a numerator, that may probe us to do further looks into the postmarket area where we have the MedSun program where we can go direct questions to facilities that are associated with it so we get numerator and denominator information. Basically, it creates a signal if you see an uptick in a period of time. That information was useful in metal on metal hips.

As far as trying to clean up the definitions, I'm going to defer

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back to the review team, Ron or one of the --

DR. JEAN: So, for our purposes, we are asking for your feedback to help us with the regulatory definitions. Some of the impact for what you decide describes DDD, and potentially this degenerative spine pathology term that we described in your panel packs, is, you know, a description within the classification itself. Again, we understand we're asking you to consider a topic that hasn't been resolved in 10, 15, 20 years.

DR. KELLY: Yes, Dr. Rohr?

DR. ROHR: Bill Rohr.

I wanted to get back a second to this issue of the dynamic non-rigid systems. And I see a problem we have, Mark, in that, you know, when we talk about the rigidity of the system, it is really the system. So it's very hard to give you a definition when I can make the rod thinner. There's lots of things I can do to take the same system and make it more flexible than a so-called flexible system. I think we also have a lot of clinical -- I mean I have enough gray hair that my days of training -- the Dwyer system was what we were taught to use in certain types of scoliosis. And I believe that's a pre-amendment device.

So I'm not so sure that the definition or this attempt to find a definition between rigid and non-rigid is valuable because there's no way to define the system as used by the surgeon as either flexible or non-flexible, even though I know manufacturers promote this issue. And I'm not so sure

we can make that differentiation, and we have a lot of history with non-rigid systems that worked fairly well in their day when they were the best we had.

So I think you have to kind of just say the systems get approved for this indication in the spine and let the clinical data -- let the clinicians through clinical data decide which ones are going to be successful or not. I mean at some point we're adding these systems to great rigidity because we think it increases the rate of fusion or correction. I mean there are other reasons to have flexible elements in there. And at some point it doesn't work or it fails, and that kind of has to be the endpoint, not some definition we can define. Because I can take the same rod and make it thinner or thicker and I can make it rigid or more flexible. And in some cases a metal rod's more flexible than say some of the polyaryletherketones. I can make those fairly rigid, if I design them correctly.

MR. MELKERSON: You've just described how manufacturers approached getting systems that were more dynamic, but it could -- if you're addressing issues, you may be able to draw distinctions between flexible and rigid, which were the original discussions in pedicle screws, could you lump them together, when we first talked about reclassification in the 1993-94 era.

The question becomes dynamic elements that are designed into the longitudinal member, springs, the inner connections between the longitudinal members, are those ways to distinguish -- again, I'm turning these back to questions, because the arguments for why they were allowed

through 510(k), they used the flexible versus rigid argument as being there's a range with metallic rod diameter, et cetera, for flexibility of the system when it's screw plus the longitudinal member. And then the question became other features that basically allowed it to move as well as be flexible.

DR. KELLY: Yes, Dr. Golish?

DR. GOLISH: Mark, I have my own thoughts on this question, but do you with your long history of leadership at ASTM believe there is a set of standards currently approved that can distinguish in the current marketplace which is rigid and which is dynamic?

MR. MELKERSON: Being the co-author of ASTM 1717, those were designed to distinguish between the rigid and semi-rigid systems, but that is not recognized as being -- as pointed out in our panel presentation, the current system -- or test methods that are recognized by FDA were not predictive of the clinical outcomes of certain dynamic systems that led to us calling for the 522 studies. So even though the tests -- it was also mentioned that some of those test methods were "modified" from ASTM 1717 to help try to address differences without addressing it with clinical information.

DR. KELLY: The clarity resides upon -- is it material, the nature of the material allowing semi-rigidity? Or are there grossly movable parts that afford what I would say, if not gross motion, appreciable motion? So we need to define that more clearly.

Yeah, actually Dr. Lyman and Irish Joe.

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DR. LYMAN: This is just a quick question. I haven't heard anything today estimating how many of these are being put in. Does anybody have any idea how often these systems are being used nationally?

UNIDENTIFIED SPEAKER: These systems meaning dynamic systems?

DR. LYMAN: No. I'm referring to all of these pedicle screw systems, whether they're dynamic or rigid. Do we know?

DR. KELLY: I think Dr. Devlin had a slide, didn't he, of some of the usage? Perhaps do we have an idea how many surgeries were performed?

DR. DEVLIN: Just -- one second.

DR. KELLY: Okay. Well, that was an off-the-cuff, but Dr. Devlin, do you want to push the microphone and just give an assessment? Is the usage also increasing?

DR. DEVLIN: I don't have an exact figure, but as an estimate I would say upwards of half a million per year in the United States.

DR. KELLY: Mr. O'Brien.

MR. O'BRIEN: Getting back to Mark and the FDA on this question about rigid or whatever, it still seems to me in my small, little mind that that becomes a problem when we start talking about construct, you know? And that becomes -- that really is the confusing factor here, the confounding factor. If we talk about anchoring systems, longitudinal

members or cross-sectional members, those are different, but if you start putting them all together and trying to define a construct versus another, you get into a very -- you know, a quagmire of issues here that become a problem because first it was the pedicle screw versus -- is the pedicle screw better? Yes, the pedicle screw, you know, has shown to perform, et cetera, et cetera, so it just seems to me that we're getting a problem.

In terms of the data, I just wanted to follow up to what was said too in terms of some of the things I see. I mean even like the Sansur's 2010 study, which was the SRS database, that is a self-reporting database, if I'm correct, which, you know, not only has the variability of time but it has the variability of the amount of reporting that's done in any given year within there. So you have a wide variability in there, and it's very difficult. You don't know what n is or anything else, so it's very hard to determine what that really is telling us, you know.

DR. KELLY: I'd like to hear from people we haven't heard from.

Ms. Whittington?

MS. WHITTINGTON: It sounds like there's a thousand ways to skin a cat, and we each use it the way we need to use it on that patient on that day. I haven't seen or heard about any collective patient outcomes that are approached in a single approach with a -- the combination of devices or a single device. Where is that information to help guide the patient as they ask questions and the provider or the physician and surgeon as they do the

cases? There are lots of different parts to each -- to some of these constructs. And so, how do you determine that?

And who's done some studies that look at what the outcomes really are when you do things in this way with this disease or another way with another disease?

DR. KELLY: Very well. Dr. Haines, is your hand --

DR. HAINES: Well, that's exactly the point. It is -- there are so many variables, there's so much complexity in trying to fit a construct to a specific patient's indication, that you must apply principles. There will never be enough data to answer that question for that specific patient. So you fall back to the principle. Is a fundamental -- is fusion an important part of treating this patient, and do I have the tools that will allow me to safely and effectively create that fusion? And then the practice of medicine beyond that is making the modifications with all the other little pieces and things that you can use to make that fit that patient's individual circumstance.

And I fear that we've gone past the safe and effective tools, and we're trying to get into the mud of irresolvable issues in direct patient care.

DR. KELLY: But, again, I made those comments earlier in the spirit of patient protection. Again, having the blessing of experience, our charge today is to really debate the safety and effectiveness -- again, we're not ethicists. It seems to me that if you're going to do this operation, this is

the best product out there.

Okay. Mark had a comment.

MR. MELKERSON: Well, I'm trying to refocus a little bit. All spinal systems are multi-component. They're made of multiple rod diameters, multiple sizes of hooks, screws, wires, cross-members, cross-connectors. Some are either -- allow you to attach it to another system. So when you're talking about pedicle screws, you can't put a pedicle screw in and expect that to fuse the spine. The only screws that I'm aware of that were used for fusion were facet screws. So when we talk about systems, they are the construct, and it's a big tray of things with multiple screw sizes, multiple rod sizes, plates, combinations thereof.

So when you're looking at the system, we have to basically define a system. You can't use a pedicle screw by itself to fuse the patient. It's going to be a mixture of components. And that mixture is going to be patient-specific. So when we're looking at systems, we look -- and I'll use the ASTM 1717 model -- they tried to define a worst-case mechanical approach with a set of four screws with a missing vertebral body to basically try to say I'm testing that system should there be no fusion. So that's a reason to look at a special control.

So when you're talking about a system, they have to -- the sponsor has to define what's the longitudinal member? What's the anchor mechanism to the spine? Are there cross-connectors to help with rotational

stability? So when you're looking at the system or construct, that's what we mean by pedicle screw spinal system. It's not just hooks versus wires versus screws. So when you're thinking of the products, they are multi-component and not -- to use a phrase that one of the previous Panel members used is they're basically a Tinker Toy set. You have to -- or erector set. You have to model that system to the patient's particular needs. So when you --

DR. KELLY: So -- from Dr. Trier?

DR. TRIER: Yes. This is Kathy Trier.

I wanted to also help to refocus the Panel on the questions today. Mark is referring to, you know, the various components of a pedicle screw system. And, essentially, what we are being asked today to do is to look at specific indications that are currently Class III and whether or not they should be reclassified to Class II. We're still talking about the same pedicle screw systems. It's the indications that we're really looking at reclassifying for the use of these -- in the use of these pedicle screw systems.

And with respect to Dr. Lyman's question about or his comment about the evidence that is reported today here in the FDA presentation, you know it's an imperfect literature review, but it is a literature review that demonstrates to me a pattern that is fairly consistent, that in comparison of the Class III indications to the Class II indications, we are seeing a very similar profile of effectiveness and also safety issues. And while it's not the gold standard of randomized control trials and it's not specifically addressing the

issues that Connie has raised, it certainly presents a pattern of results that to me demonstrates a reasonable assurance of safety and effectiveness.

DR. KELLY: Can I pose a question to some of our sponsors?

Dr. Haines, when would you use a flexible system? What are indications to augment a fusion? Are there any?

DR. HAINES: I think the ideas behind the flexible systems are very interesting, and I'm not -- I don't think we're at the point where we can be very definitive about them.

DR. KELLY: Okay. Dr. Pfeifer's had his hand for about 20 minutes up, so --

DR. PFEIFER: Well, you know, I've got this problem with my right arm, it jumps up, but to Dr. Lyman's question --

DR. KELLY: We have drugs for that.

DR. PFEIFER: -- the BMED database that Medicare keeps can give you some idea of the number of times CMS paid for 22842 code, which is the insertion of a spinal fixation device three levels. And those numbers for just that, you know, two to three levels run in the 50,000 range. That's only Medicare patients. The other place you can try and get your data from, if you know the DRG for posterior spinal fixation, which is I think separate from anterior and posterior spinal fixation, the recently published CMS data -- again, it's Medicare data on hospital charges -- has the n , the number that each hospital is doing. Unfortunately, you have to take state by state and add

it up, but that's the best I have for you on that one.

As to Dr. Whittington's questions, the problem with getting efficacy data is how do you want to do it? Prospective randomized non-crossover, you're randomly assigned to a fusion with or without. We can't do that in the United States. The closest we come is the Dartmouth data. And if you look at the data on grade 1 and grade 2 spondylolisthesis, that's the best I think that we've got out there. Look up Weinstein and see what it tells you.

DR. KELLY: Dr. Lehman?

DR. LEHMAN: Ron Lehman.

I think the -- one of the basic issues -- I mean certainly, you know, listening to the 1717 stuff, is it too cursory to say if we're going to differentiate between rigid and dynamic type systems that we're going to say -- obviously the system is the system. There's multiple fixation points, types of metal, diameters, types of screw heads or tulips. Is it safe to say that a dynamic system is one that does not intend for immediate rigid stability?

I guess, Mark, maybe that may be a more direct question for you. Is that a reasonable distinction to make?

MR. MELKERSON: I'm going to defer the question because I believe there's activities at ASTM, and Dr. Golish may be more attuned to what's going on, but they are trying to develop standards for the dynamic, intentionally dynamic systems.

DR. KELLY: I think just from an overview, Mark, it's a materials question versus a mechanical question. I think if the mechanism of the implant allows motion, that's a distinction between materials or semi-rigid. So I think as -- I propose that we -- to move forward today, we can at least adopt that working definition.

Dr. Golish, any gross objections to that?

DR. GOLISH: No. No gross objections. And getting to Mark's point and Dr. Lehman's point, those efforts are certainly continued, but as I said, at the start I think it's at least conceivable that special controls can differentiate those two in principle.

DR. KELLY: Okay. Dr. Lehman?

DR. LEHMAN: Ron Lehman again.

Just I guess to follow up with your initial question, when we use dynamic stabilization, I think the indications are relatively small. Although it's an interesting concept, the spinal segment is much different than, you know, actual skeleton and those types of things. There's certainly been, you know, many indications espoused for this dynamic technology in a fusion intended situation, but I think the literature -- the evidence in the literature currently is not at the same level as it is with rigid type fixation systems.

DR. KELLY: Joe?

MR. O'BRIEN: I'd just like to get back to something earlier that Dr. Haines had brought up and with Dr. Bechtold and ask the question in

terms of the special controls that are being recommended that they only were focused on performance controls and primarily -- labeling, actually was the primary control -- as opposed to postmarket surveillance controls and why that decision's made? Why there isn't postmarket surveillance controls that would be indicated there?

DR. KELLY: If the FDA requires some time to deliberate this, we can address this later on, if you think you need some time?

MR. O'BRIEN: And while they're taking time, I guess I would ask the basic question. I probably know the answer to this, but it does seem like there is going to be an ever changing amount of whatever that construct is, whatever the Tinker Toy toolbox is that we want, but there's always going to be indications of problems later. You know, it seems to me again rather simple that, you know, having a patient registry would be a great way to track these and follow and to see whether or not everything's following, but we never come up with patient registry.

And I'm just curious as to -- is that a cost issue or not considered to be a good way to just track all of this on a regular basis?

DR. KELLY: I think cost is usually the big issue, Joe. And I think the joint surgeons are way ahead of the curve than the rest of us sports and foot and ankle specialists.

Ms. Bechtold, you have a clarification?

MS. BECHTOLD: Just to follow up with that -- this is

Stephanie Bechtold. Our Office of Surveillance and Biometrics are always open to a discussion about establishing registries for this population, but for the current Class II indications for the same pedicle screw spinal systems, we do not currently use postmarket studies or registries as a special control.

DR. KELLY: There's time for a couple more questions, and I would like to get to the open hearing, you know, shortly, so Dr. Pfeifer?

DR. PFEIFER: Again, that -- full right hand. The American Academy of Orthopaedic Surgeons tried to put together a MODEMS system in the year 1990 -- I was involved with that -- with outcomes database. The issues were not necessarily cost, although they certainly were -- you know, doing it as a member benefit would cost a lot buying in. Nobody wanted to pay for it. But there are a myriad of legal issues, patient confidentiality, who reports the outcomes, who has access to the data, who controls the data, and they gave you a list a mile long.

And that's why it's not caught on yet, although North American Spine is back to trying it again for the spine. The arthroplasty people have their database up and running. These are not all-inclusive databases, meaning that it's voluntary reporting, but with the stimulus on the payment side that participation in the database will probably count as a quality measure and you get that extra 2 or 5%, or whatever CMS is trying to come up with, you may see more registries in the future.

DR. KELLY: IF there's no further questions for FDA, I would like

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to recommend a break. We can reconvene in approximately 15 minutes and commence our open public hearings. Thank you.

(Off the record.)

(On the record.)

DR. KELLY: It is now 10:47. I'd like to resume this Panel meeting. We'll now proceed to the Open Public Hearing portion. This is where public attendees are given the opportunity to address the Panel and present data, information, or views relevant to the meeting agenda.

At this point Lieutenant Commander Anderson will now read the Open Public Hearing disclosure process statement.

LCDR ANDERSON: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the 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 speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship 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 the 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.

DR. KELLY: Thank you.

There have been four requests to speak. Okay. We will go over the process of the speakers' protocol to ensure a smooth transition.

Each speaker will be given 5 minutes to speak. Please pay attention to the timer at the podium. A yellow light will appear when there is one minute remaining.

Please be sure to state your name, company, and any financial disclosure. Again, public attendees may not participate except at the specific request of the Panel chair.

The first speaker this morning will be Dr. William Welch. Could you please come forward to the microphone? We ask that you speak clearly and allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting.

Thank you, Dr. Welch.

DR. WELCH: Dr. William Welch, University of Pennsylvania, Pennsylvania Hospital. I have no disclosures or financial relationships having anything to do with the session this morning. I'm representing the American Association of Neurological Surgeons and the Congress of Neurological Surgeons. Just a very brief statement.

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Based on my calculations, based on the information that I knew and heard this morning, the surgeons -- spine surgeons have implanted about a million of these implant systems over the past 25 years or so. I personally -- and I know that the AANS and CNS believes that these are safe devices. We strongly believe that for the indications of degenerative disc disease in spondylolisthesis, other than severe spondylolisthesis grade 3 or 4, and for degenerative spondylolisthesis without objective evidence of neurological impairment, the devices should be changed to Class II.

I can tell you as a practicing surgeon, until this issue was brought up, I would suggest that I didn't personally know that these were Class III, and I would suggest that most physicians did not realize that these were Class III. And just my poll of my colleagues, everyone agreed uniformly that a down-classification would seem appropriate. Thank you.

DR. KELLY: Thank you, Dr. Welch.

Our next speaker will be Dr. Martin Yahiro.

DR. YAHIRO: Mr. Chairman, ladies and gentlemen of the Panel, and members of the FDA staff, good morning. My name is Martin Yahiro. I'm an orthopedic surgeon employed by NuVasive, Incorporated as the Director of Medical Affairs.

On behalf of NuVasive, I would like to thank you for this opportunity to make a few remarks regarding your deliberations on the pedicle screw spinal systems before you.

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First, I would like to thank the Panel members for taking the time to provide this important service to the FDA, the medical community, and the patients we all serve.

Back in the mid-1990s when pedicle screw spinal systems were first considered by the FDA for reclassification, members of the 1993 and 1994 Orthopedic and Rehabilitation Devices Advisory Panels were asked to provide their medical and scientific expertise on pedicle screw spinal systems in an extremely hostile legal environment. Under mounting external pressures and at significant personal costs, those Panel members provided FDA with sound recommendations that have stood the test of time. We all owe those Panel members our gratitude for their courage and scientific integrity.

During the February 1993 panel meeting, FDA requested that orthopedic professional societies and spinal implant manufacturers submit to FDA available valid scientific evidence on the performance of pedicle screw spinal systems. In response, with extensive input from FDA, the historical cohort study was designed to collect safety and effectiveness information on patient populations with two distinct diagnoses: degenerative spondylolisthesis and fractures.

These two indications were chosen to encompass the clinical and biomechanical extremes, those patients with longstanding pain and neurologic deficits, and those with the loss of mechanical support of the

anterior column because of trauma. It was intended to provide data to reclassify all diagnostic indications since the worst-case clinical and biomechanical indications were included in the clinical dataset.

At the July 1994 panel meeting, the Panel recommended that FDA reclassify the generic type of device from Class III to Class II when intended for the treatment of degenerative spondylolisthesis and spinal trauma. The indications in the proposed rule read acute and chronic instabilities and deformities such as trauma, tumor, or degenerative spondylolisthesis.

However, the final rule was unnecessarily complicated and limited the diagnostic indications to provide immobilization and stabilization of the spinal segments in skeletally mature patients as an adjunct to fusion in the treatment of the following acute and chronic instabilities or deformities of the thoracic, lumbar, and sacral spine: severe spondylolisthesis grades 3 and 4 of the L5-S1 vertebra, degenerative spondylolisthesis with objective evidence of neurologic impairment, fracture, dislocation, scoliosis, kyphosis, spinal tumor, and failed previous fusion or pseudarthrosis.

These indications exclude patients with spondylolisthesis grades 1 and 2 and those without neurologic deficit and exclude degenerative spinal stenosis and degenerative disc disease.

We would like the Panel to consider whether pedicle screw spinal systems should be Class II for any diagnostic indication for which

immobilization and stabilization of the spine as an adjunct to fusion is clinically indicated.

NuVasive would like to propose the following wording for consideration: The device is intended to provide immobilization and stabilization of the posterior thoracic, lumbar, and sacral spine as an adjunct to fusion in the treatment of degenerative conditions resulting in disc herniation, spondylolisthesis, and stenosis; deformity, including scoliosis, kyphosis, and lordosis; instability secondary to trauma or tumor; and iatrogenic conditions, including failed previous surgery and pseudarthrosis.

This slide shows the side-by-side comparison of the current diagnostic indications on the left and the proposed wording on the right.

Thank you for your consideration.

DR. KELLY: We're going to ask questions at the conclusion of the presentations.

Thank you, Dr. Yahiro.

The next speaker is Dr. Susan Krasny.

DR. KRASNY: Good morning. My name is Dr. Susan Krasny. I'm speaking on behalf of OSMA, of which I am the past president, and I currently serve on the board of directors. I am also the Vice President of Regulatory Affairs for Stryker Corporation, a company that makes products subject to today's panel.

Founded in 1954, OSMA is a trade organization whose

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membership consists of manufacturers of orthopedic surgical appliances, implants, instruments, equipment, and orthobiologics.

In 2009 OSMA filed a petition seeking reclassification of traditional rigid pedicle screws for degenerative disc disease from Class III to Class II. OSMA fully supports FDA's recommendations for reclassification of these devices.

I will provide first a summary of OSMA's 2009 petition, including published literature, followed by MAUDE review, and then review proposed regulatory controls.

FDA's 1998 classification of pedicle screws included use as an adjunct to fusion with Class II indications, as noted in the black text. Class III indications shown in red included DDD and spondylolisthesis not classified as Class II. OSMA's petition seeks to reclassify these Class III indications for pedicle screw systems as Class II. From here forward, for simplification, I will refer to this as DDD.

As shown for the proposed reclassification, OSMA recommends inclusion of DDD as Class II for pedicle screws, and as shown on the slide, we noted the spinal system 510(k) definition of DDD. However, we look forward to the discussion on the more encompassing term degenerative spinal pathology, as proposed by FDA. In addition, OSMA also recommends for simplification consolidation of the spondylolisthesis indications and, for consistency with the current Class II designation, removal of skeletally mature

bone.

Since the first 510(k) clearance for pedicle screws for DDD in 2003, approximately 383 510(k)s for approximately 65 companies have been cleared. For its 2009 petition, OSMA conducted a literature search and review using PubMed articles published over a 15-year period through May of 2009. Studies had to include pedicle screw use for DDD with safety and/or effectiveness data on 15 or more subjects.

Nineteen studies with results from 1,087 patients were identified. A majority of the studies included two or more years of patient follow-up. For purposes of comparison, results from these studies were contrasted to Dr. Yuan's 1994 publication in *Spine* for patients with spondylolisthesis and neurologic deficit treated with pedicle screws, a Class II indication. Fusion rates exceeded 90% in the majority of studies. Improvements in pain and function were reported. The results of patients with DDD were comparable to those as described by Yuan.

For the 2009 petition, as illustrated on this slide, the risks to health for pedicle screws for DDD were identified based on the complications reported in the published literature. The types and rates of device complications for DDD were comparable to Yuan's results.

As reported for spinal surgery in general, other risks for pedicle screw use include neurological and wound adverse events. For these events, again, there were no apparent differences for the patients treated versus

Yuan's results.

In preparation for today's meeting, OSMA identified 15 additional publications since the 2009 petition. Two studies are especially noteworthy. Phillips et al. published a systematic review of the literature with 26 studies and 3,060 patients. Robinson et al. reported results from a registry of 1,310 patients. Both studies included three fusion technique groups of which one group was pedicle screws. The literature reports were consistent with our 2009 findings.

OSMA conducted a MAUDE review for events reported from 2005 to '12 for pedicle screws for three groups of indications. One included Class III DDD with product code NKB. The other two groups included Class II indications with one for spondylolisthesis MNH and other MNI. The types and rates for events for NKB appeared similar to Class II product codes.

General and special regulatory controls that have been applied to Class II pedicle screw uses for 15 years are relevant to reclassified Class III pedicle screw use. The general controls include manufacturing, establishment registration, quality system regulation, labeling requirements, record keeping and reporting related to adverse events and recalls. Special controls to mitigate any risk associated with the use of pedicle screws for DDD include performance standards such as material, mechanical testing and biocompatibility, and other appropriate labeling information.

OSMA believes that the information presented provides

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reasonable assurance of safety and effectiveness of pedicle screws for DDD. General and special controls are appropriate to ensure safe use of pedicle screws. Class II is an appropriate classification.

OSMA wishes to thank the Panel and the FDA for their efforts today, and we look forward to the deliberations.

DR. KELLY: Thank you, Dr. Krasny.

Our last speaker will be Dr. Diana Zuckerman.

DR. YTTRI: Good afternoon. I'm actually Dr. Jennifer Yttri, and I'm speaking today on behalf of the National Research Center for Women and Families, of which Dr. Zuckerman is our president.

Our organization does not accept funding from device manufacturers, and therefore, I have no conflict of interest today.

Our nonprofit research center includes scientists and medical and public health experts who analyze and review research on a range of health issues. We respect the work of the FDA, and our president, Dr. Diana Zuckerman, serves on the board of two nonprofit organizations dedicated to providing the FDA with the resources needed to do their job.

Over the past dozen years we have provided comments to the FDA regarding the classification of medical devices. We have extensive knowledge of the processes involved in reviewing new medical devices, but our primary concern is public health and making sure that patients and their physicians have accurate, objective, and understandable information about

medical products on the market.

The patients being discussed today have low-grade spondylolisthesis, or DDD, and their reduced clinical severity means that their benefit-to-risk ratio is very different from patients with more severe disease that this committee has previously considered.

The risks using traditional rigid pedicle screw spinal systems are similar regardless of the severity of diseases. Although the risks seem to be low, they still are serious, and these risks must be compared to the proven benefits. Is the outcome of surgery better or worse without the pedicle screw system?

I'm not talking about comparative effectiveness to other devices, but it is essential to prove that this device used in surgery is better than surgery without the device. Spinal fusion rates might be better, but there is no clear benefit on factors that are important to patients such as reduced pain and increased function.

In the absence of clear evidence that the pedicle screw systems benefit patients, why subject the patient to any increased risk for questionable benefit? They're certainly worse in terms of safety than nothing. Currently, the pedicle screw systems on the market that have been used for years don't seem to do much harm whether or not they do much good. However, your advice today will influence FDA's decision applying to manufacturers making any of these systems in the future.

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By definition, pedicle screw systems used with spinal fusion are a high-risk device because they can sustain life or make it miserable. The law therefore states that these Class III devices should be subjected to testing and clinical trials. And while pedicle screw systems currently on the market may be safe and effective, the classification of these devices will affect new products. And without clinical trials, we don't know if those are safe or effective.

If the FDA down-classifies these systems, as proposed, new pedicle screw systems made in the future will not be required to be tested in clinical trials to make sure they are safe and effective. The only testing required would be biocompatibility, sterility, and mechanical testing controls for a Class II device. There has been extensive discussion today as to the -- how variable these "equivalent" devices are. And so, mechanical testing and labeling controls are insufficient substitutes for measuring what happens in a patient.

All of us want patients to have access to medical devices and procedures that are safe and effective. You may be confident that the pedicle screw systems currently available are safe and effective, but none of us can know whether new devices made in the future by other companies or using new designs will also be safe and effective. Please protect patients and their physicians by urging the FDA to require clinical trials for these systems. This should be done through the PMA process, as a Class III device would indicate.

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Or if you prefer compromise, you could recommend that clinical trials or testing be required as a special control with the Class II device.

The bottom line is clinical trials are needed to ensure these screw systems are safe and reasonably effective. Thank you.

DR. KELLY: Thank you, Dr. Yttri.

At this point I would like to ask if the Panel members have any questions to the open public forum presenters? Any questions?

Yes, Dr. Pfeifer?

DR. PFEIFER: Dr. Yahiro, in your list of indications, you suggested disc herniation. And we're going to be discussing disc degeneration, and if you look at that global picture of disc degeneration, disc herniation probably falls somewhere near there. Now, I understand there may be specific indications in terms of failed surgery, but that becomes a different animal.

Can you comment a little bit on what you see the indications for purely a herniated disc in a patient with radiculopathy, which is the typical disc herniation I would think of when I see disc herniation?

DR. YAHIRO: Martin Yahiro.

The intent of that was to identify degenerative disc disease as a spectrum of diseases, and on the maybe more mild side would be the herniation and maybe on the far end would be degenerative stenosis or deformity. And I imagine some patients may require, for example, a TLIF and

would require a pedicle screw fixation for that.

DR. KELLY: Are you satisfied with that answer, Dr. Pfeifer?

DR. PFEIFER: Thank you. Well, I guess my concern is -- and I don't know whether I'm allowed to introduce this, but I sat on another panel that was talking about the dynamic systems, and in European studies they were using it to treat simple disc herniation. And this is where we come into protecting the patient, or at least -- I don't know whether we should protect the patient, how much you want to rely on data, membership, teaching that the academies do and what have you.

But if you put just disc herniation as an indication, there might be some expanded use that I'm not sure I would agree is something I would want if I had a purely herniated disc. And that will probably carry over into the discussion of degenerative disorders and how specific do you want to get.

Now, again, if I go back to the North American Spine classification, which, you know, is not just David Fardon, but which was a consensus panel of presumed experts in 2005, if you look at their disc degeneration discussion, it includes this degenerative disc disorder, kind of. It's a term. It doesn't use that term specifically, but you could argue that just using their definition of degenerative disc would be degenerative disc disorders.

But included in that is a disc -- I don't know a normal disc that herniates. They do. I mean it's very rare. The neurosurgeons can correct me

if I'm wrong, but the biomechanical studies I know, if you take a bone -- this bone construct off to the lab and load it to failure, what fails is the bone, not the disc. So in order for the disc to rupture, it has to have been started down this degenerative process. Usually typically it's an annular tear, following which you get the split and the extrusion. And you've had more than one patient who came to you who said, well, I just bent over, I twisted, I turned, I did nothing, and the next thing I know I got this leg pain.

So I'm a little bit sensitive to the term disc herniation per se. I admit that I'm from Boston, and we're just starting to put celery stalks in our Bloody Marys at this time, so we tend to be a little bit conservative in our approach.

DR. KELLY: Good answer.

DR. PFEIFER: But, I --

DR. KELLY: I think -- Dr. Pfeifer, I understand where you're coming from. I think that that's going to fall into our discussion of the definition. I think this is really in the realm of non-radicular symptoms of the application, but I understand. Your point is well taken. I think we can debate that in deliberations on the definition of DDD.

Any other questions for our presenters?

Very well. At this point, I'd like to proceed with the focus of our discussion on the FDA questions. Copies of the questions should be in your folders.

I wish to remind the Panel that this is deliberation period among the Panel members only. Our task at hand is to answer the questions based on the data that you heard this morning and in the panel packs and the expertise around the table that you've heard as well.

With this said, I'd ask each Panel member identify him or herself each time he or she speaks to facilitate transcription. And I would like to hear from everyone, if they feel so moved.

Please show the first question, Dr. Kavlock.

I guess before we proceed, is there a need for further deliberation? Anyone wish to ask a few questions amongst ourselves or make comments? Not directed at the FDA per se, but is everyone comfortable proceeding to the questions?

Okay. Dr. Kavlock, you may proceed. Thank you.

DR. KAVLOCK: Okay.

At this time we'll be asking the Panel to comment on several questions related to the information we presented earlier. Each question will be asked separately after a brief review of the FDA's classification system.

As introduced earlier, the FDA uses a three-tiered classification system based on the level of risk and the controls needed to provide a reasonable assurance of safety and effectiveness. And it's important to note that a device should be placed in the lowest class whose level of control provides a reasonable assurance of safety and effectiveness.

A device is considered low risk in Class I when general controls alone are sufficient to provide a reasonable assurance of the safety and effectiveness of the device. Class I devices are usually exempt from requiring submission of a 510(k). Examples of Class I devices include general manual surgical instruments.

A device is deemed moderate risk in Class II when general controls alone are insufficient to provide a reasonable assurance of safety and effectiveness, but sufficient information can be established using special controls. Examples of special controls include performance data requirements such as clinical and/or nonclinical data. Class II devices typically require submission of a 510(k). Examples of Class II devices are intervertebral body fusion devices or anterior spinal plates.

A device is deemed high risk and Class III eligible when there is insufficient information to determine that general and special controls are sufficient to provide reasonable assurance of safety and effectiveness, and if it is life-supporting or life-sustaining, or for 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. Class III devices generally require submission of PMA, and examples of Class III devices are non-fusion technologies such as total discs.

With regard to the classification process, the FDA relies only upon valid scientific evidence to determine whether there is reasonable

assurance that the device is safe and effective for its stated conditions of use. As defined in 21 C.F.R. 867, valid scientific evidence includes evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience.

Question 1: The FDA has identified the following risks to health for traditional, rigid pedicle screw spinal systems based upon the input of the original classification panel, review of industry responses to the 2009 515(i) Order, the Manufacturer and User Facility Device Experience or MAUDE database, and FDA's review of the medical literature:

Malposition, implant loosening, device breakage, device malfunction, disassembly, bone fracture, graft settling or displacement, loss of correction, pseudarthrosis, bleeding or vascular injury, neurologic injury, back/leg pain, dural injury/CSF leak, wound problems, infection or sepsis, skin irritation, cardiac, respiratory, gastrointestinal, revision surgery, or death.

Is this a complete and accurate list of the risks to health presented by traditional rigid pedicle screw spinal systems? Please comment on whether you disagree with inclusion of any of the risks or whether you believe that other risks should be included in the overall risk assessment of pedicle screw spinal systems. Risks associated with dynamic stabilization systems for fusion will be discussed later in Question 4.

DR. KELLY: Thank you. It's a pretty exhaustive list, but any

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members wish to make some additions, comments?

Actually, yes, Bill.

DR. ROHR: Bill Rohr.

You know, we face this from time to time, but I think particularly in these devices, there's a list on here including wound problems, infection, skin irritation, cardiac, respiratory, and the rest of that list, all except for revision surgery I think are -- there's nothing about these devices that inherently makes those risks specific to the device, and I don't think they belong on the list. They're inherent to the operation, but not specifically to these spinal implants.

So I know we had this discussion many times, but again I'd like to reiterate, I don't think they should be listed as specific complications of these devices.

DR. KELLY: Yes.

DR. LYMAN: Stephen Lyman.

I had a question for clarification on that. Do these procedures take longer than a non-instrumented fusion? So that could lead to increased infection risk, so I guess from that perspective it would be the use of these devices that would increase infection. I would agree for things like respiratory, gastrointestinal that these -- the fact that you're operating may be what's causing that, but not what exactly you're doing during the operation.

DR. KELLY: Plus it's a foreign body. So infection is already listed there, Steve.

DR. LYMAN: I was just responding to --

DR. KELLY: Oh, I see.

Yes, Dr. Graf?

DR. GRAF: Specific to the graft settling and displacement, again, that might be a sequelae of implant loosening or device breakage, but I don't think that's inherent to the pedicle screw construct. And I don't know if that should be included. Second, I don't see on the list any allergic reaction, metal allergy, et cetera, which could potentially be -- if we're going this broad to have respiratory and gastrointestinal and death, that might be included as well.

DR. KELLY: I'd like to hear from our Patient and Consumer Representatives. Ms. Whittington?

MS. WHITTINGTON: I think anytime a patient has a complication of something, that they need to be aware that they could have a wound problem, or they can have maybe an issue with metal. I can't say that it would be on the skin necessarily. It is an exhaustive list. It's everything.

DR. KELLY: Mr. O'Brien?

MR. O'BRIEN: I would agree with Dr. Graf that I think allergy is something certainly with patients come up. And, you know, we discussed earlier the issue about adjacent segment. Notwithstanding what Dr. Lehman

had indicated with the studies or whatever, we do have a lot of patients that seem to indicate that that's the diagnosis that they've been given from their surgeons, that that's the fundamental issue that they're having revision surgery for. So to me it seems to be an inherent risk that that is at least explained that way.

DR. KELLY: Okay. But there's no harm in including that.

Dr. Trier?

DR. TRIER: I agree with the list and the comments that have been made so far.

DR. KELLY: Yes, Dr. Lehman?

DR. LEHMAN: Ron Lehman.

I think one of the reasons we probably should keep gastrointestinal, respiratory, and cardiac, not necessarily just as systemic potential effects or systems that could be deleterious from a surgery period -- there's a potential risk of misplaced implants. We certainly have made -- there's studies in literature about case reports of, you know, errant screw placement causing some of those issues. And so, I think for those reasons, they have to be listed or should be listed as potential complications, more from that than any systemic effect.

DR. KELLY: I suppose that need for implant removal is inclusive in, I guess, irritation and fracture, device malfunction. I just thought of that. Do you believe that is inclusive in those terms?

Anyone else have some comments on what we should include perhaps or delete?

Mr. Melkerson?

MR. MELKERSON: I want to make sure that you focus in on the last part of the question, which is, is there a difference between whether we call it rigid or semi-rigid systems than dynamic stabilization?

UNIDENTIFIED SPEAKER: That says in Question 4.

DR. KAVLOCK: No, it's the last --

DR. KELLY: I think -- what I'm reading here, Mark, it seems like that's going to be addressed a little later. I'm reading it about the addition/deletion of these risks that are listed as the principal aim of this question, so without further comment, I'd like with the Panel's permission take a stab at answering this.

I think that with respect to Question No. 1, it is the Panel's consensus that this is an overall comprehensive list. There are some concerns that the inclusion of allergic response is also necessary.

Mr. Melkerson, is this a sufficient answer?

MR. MELKERSON: At this time, yes.

DR. KELLY: Thanks for that vote of reassurance.

(Laughter.)

DR. KELLY: Okay. Could we have Question No. 2, please?

DR. KAVLOCK: According to 21 C.F.R. 860.7(d)(1), "there is

reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury association with the use of the device for its intended use and conditions of use." In addition, according to 21 C.F.R. 860.7(e)(1), "there is a reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results."

The FDA believes that the available scientific evidence supports a reasonable assurance of safety and effectiveness of traditional, rigid pedicle screw spine systems when intended to provide immobilization and stabilization of spinal segments as an adjunct to fusion in the thoracic, lumbar, and sacral spine as an adjunct to fusion in the treatment of degenerative disc disease and spondylolisthesis other than severe spondylolisthesis (grades 3 and 4) at L5-S1, or degenerative spondylolisthesis with objective evidence of neurologic impairment.

Do you agree that the available scientific evidence is adequate

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to support the safety and effectiveness of traditional, rigid pedicle screw spinal systems for these indications for use?

DR. KELLY: Thank you.

Remember we're going to confine our discussion to those two indications, DDD and other spondys. And the two main issues at stake are do we agree or not agree that the available evidence is adequate to support to the safety and effectiveness of rigid pedicle screw systems for those above indications?

Any dissenters to that comment? No?

The second part of the question is, the Panelists -- either we believe or not believe that the probable benefits to health from the use of these traditional, rigid pedicle screw systems for use outweigh probable risks to health.

So in consensus? I know Dr. Lyman had some reservations about the quality of the data showing clear benefits. Do you amend your feelings, Steve, at this point?

DR. LYMAN: I still have those concerns about the data, and I guess what I'm unclear about is whether or not there will be an opportunity for recommending postmarket surveillance going forward. I don't think that -- I don't know that we need to require PMA of all these devices prior to their continued use, but postmarketing surveillance -- you know, some sort of clinical data about these I think would be good.

DR. KELLY: I think we could address it later, but in terms of the spirit of this question, are you reasonably comfortable with saying that the benefits outweigh the risks?

DR. LYMAN: From what I've seen and what I understand, I would certainly agree for spondylolisthesis. I'm not so convinced about degenerative disc disease, partly because of our definition, which seems pretty vague.

DR. KELLY: I'm again with you.

Yes, Dr. Pfeifer?

DR. PFEIFER: Dr. Pfeifer.

Just a question on the wording. This says grade 3 and 4 spondylolisthesis. Are we going to have another question that asks for grade 1 and 2 spondylolisthesis?

DR. KELLY: This is falling --

DR. PFEIFER: Am I reading something wrong? I'm an engineer by background, so I could be reading it wrong.

DR. KELLY: Yeah, well, we have remedial English lessons. No, it's -- other would be the grade 1 and 2.

Yes, Dr. Lehman?

DR. LEHMAN: Ron Lehman.

Maybe just another quick comment, too. I think inherent in this as well when we talk about safety and efficacy is the ability to teach

these techniques using these systems if they're Class II versus Class III. And I think that's a significant adjunct, you know, to all these things in addition to the questions that are posed here as well. If they're not Class II, we can't teach these or these can't be taught in courses. People won't learn how to use them as well, and I think that's an important part of the safety and efficacy in addition to, I think, the preponderance of literature that's out there right now.

DR. LYMAN: Sorry. Can you clarify that? You can or cannot teach which level?

DR. LEHMAN: Correct. You cannot -- similar to the Panel that we convened in the fall, if it's not on label use for indication, you can't teach it in a course, whether it's industry or not industry sponsored. As a result, one could pose that the surgeons instrumenting, you know, spines without adequate teaching because it's not allowed, is not going to be as good as people that were taught to it properly.

DR. LYMAN: And was it Class III or II that you cannot teach? That's what I'm not clear on.

DR. LEHMAN: Three.

DR. LYMAN: So if it's Class III, you cannot teach it? Okay.
Thank you.

DR. KELLY: Yes, Dr. Trier?

DR. TRIER: I wanted to respond to the last comment that

Dr. Lyman made about postmarket surveillance. And I think it's important to say at this point that there is postmarket requirements that fall under the auspices of other regulatory bodies. The group here are the premarket people, and there are postmarket people. The Office of Surveillance, the OSB group, is definitely responsible for the postmarket surveillance requirements.

So there are already postmarket surveillance requirements for any of these devices that end up being cleared or approved for the U.S. market. One of those -- and a comment that has been made multiple times about the voluntary nature of the MAUDE database. And I wanted to just simply share -- I'm sure you all are aware of this, but, you know, as one of the requirements from industry -- and being the Industry Representative I feel I need to say this, that, you know, all industry is inspected for quality systems by FDA through the Office of Compliance. And as part of that inspection, there is a review of the postmarket requirements for reporting to the MAUDE database. So when we say it's voluntary, it is voluntary. However, industry is inspected for the requirements under the QSR regulations.

DR. KELLY: Mr. O'Brien and Ms. Whittington, I'd like to hear your comments before you weigh in on this answer.

MR. O'BRIEN: I'm sorry. Say that again?

DR. KELLY: I wanted to hear from the Consumer and the Patient Representatives.

MR. O'BRIEN: On this particular issue.

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DR. KELLY: Yes.

MR. O'BRIEN: Well, first to the postmarket surveillance and what was just indicated there, I still share with -- because it does look as you -- what we're asked to point out here is that whether or not we're going to have specific controls. And those specific controls include performance controls on postmarket. I would still tend to agree with Dr. Lyman, if that's the case, then it is the purview of this Panel to say whether or not they want to be inclusive of those particular controls with this issue. So I still fall -- notwithstanding what you just indicated, I would still fall within the area of -- with Dr. Lyman in agreement with that.

And we still do have the issue of what DDD includes in that definition, so I'm still a little bit worried about that. I do think that the comment that Dr. Lehman just indicated is probably for a patient perspective. One of the most important parts -- and it gets back to what I said before. I'm not so worried about the device. It's the use of that device and the fact that it -- you know, having it as a Class II and not allow it to be -- you know, for training and education I think is a fundamentally important point to do that. So I feel much more comfortable with that in mind in terms of going ahead.

DR. KELLY: Do you have a comment, Dr. Haines?

DR. HAINES: Yeah, I share Dr. Lyman's concern about the quality of the data on a very high level of data quality. But the definition of valid scientific information that is allowed to be used to answer this question

allows the kind of data that we've seen. And based on that data, I believe that this is appropriate.

DR. KELLY: So would it be reasonable to say that perhaps you have some reservations about the efficacy for DDD, but on the whole for the other spondys, that we feel comfortable with these recommendations?

Carl?

DR. GRAF: My only concern is that are we -- we're answering a question that we're still going to define in a later question about if we're going to call it DDD or are we going to call it degenerative spinal pathology. So I just think that that might be confusing. We're trying to answer a question based on a definition which we're going to define later.

DR. KELLY: Okay. Let me take a stab at this then. And I would call on Dr. Pfeifer's English skills to help me with this.

It is the -- with regard to Question No. 2, the Panelists are essentially in agreement that the scientific evidence is adequate to support the safety and effectiveness for rigid pedicle screw systems for indications of other spondylolisthesis, but the Panel has some concerns about the benefits inherent in the application of this technology for degenerative disc disease and seeks further clarification of the definition thereof.

Mr. Melkerson, is this a satisfactory answer?

MR. MELKERSON: Yes, at this time.

DR. KELLY: Thanks again, Mark, for that little vote of

confidence.

Okay.

UNIDENTIFIED SPEAKER: We're doing the best we can, Captain.

DR. KELLY: Question --

DR. KAVLOCK: 2b. No.

DR. KELLY: Okay.

DR. KAVLOCK: Yes, so Question 3.

FDA believes that the special controls (labeling, biocompatibility, sterility, and mechanical testing) can adequately mitigate the risks to health for traditional, rigid pedicle screw spinal systems when intended to provide immobilization and stabilization of spinal segments as an adjunct to fusion in the thoracic, lumbar, and sacral spine for the treatment of degenerative disc disease, and spondylolisthesis other than severe spondylolisthesis (grades 3 and 4) at L5-S1, or degenerative spondylolisthesis with objective evidence of neurologic impairment. FDA believes the special controls also provide sufficient evidence of safety and effectiveness.

Do you agree that these special controls are adequate to mitigate the risks to health for traditional, rigid pedicle screw spinal systems for these indications for use? Please comment on whether you disagree with the inclusion of any of these special controls, or whether you believe any other special controls are necessary.

DR. KELLY: Thank you

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Mark, does postmarket surveillance fall under the category of special controls?

MR. MELKERSON: My understanding is you can have postmarket surveillance, but I'm not aware of anybody using that -- have we used postmarket surveillance?

So today we have not used it as a special control, but it's not out of the realm of possibilities.

DR. KELLY: Okay.

Yes, Dr. Rohr?

DR. ROHR: Bill Rohr.

I think these are adequate. They're used in -- these are the same controls we basically have in all other major implants like total joint implants, et cetera. They've proven adequate in those areas, and I think they'll prove more than adequate in this area.

DR. KELLY: Dr. Graf?

DR. GRAF: Again, with the same -- I do agree with the same caveat as I just mentioned about we're trying to answer a question of something that we still have yet to define in terms of the degenerative disc disease.

DR. KELLY: And I also would like Dr. Lyman to weigh in.

DR. LYMAN: I'm skeptical. The labeling was the special control for virtually all of the potential risk, as I understood from the slides that we

saw. That was sort of yes to everything, but how effective is labeling relative to actually having clinical data to demonstrate safety?

DR. KELLY: Let's hear from Dr. Jean first, please. Thanks.

DR JEAN: Hi. Ronald Jean.

Just to clarify, that's a very good point that Dr. Graf has brought up. What we tried to convey in our presentation is that given the varying definitions right now for DDD, we still believe that the evidence showed, you know, there was a reasonable assurance. The safety and effectiveness, I know you answered that question, but similarly for the special controls, we're asking you to consider sort of what we presented in the totality of definitions right now. You can refine and comment on the definitions later on.

One last point I'll just identify is, as Dr. Rohr pointed out, the special controls proposed are similar to what we currently use for the Class II indications. Thank you.

DR. KELLY: Dr. Rohr again?

DR. ROHR: Yeah, that's the point I wanted to make for Dr. Lyman. Mechanical testing is a major part of it as long as they're Class II. I don't think anybody here is suggesting these go to Class I, but as Class II mechanical testing would be required and that's pretty well -- again, the ASTM and other people are working on that.

DR. LYMAN: I mean, you did mention that these controls worked well in other settings, and you brought up total joint replacements,

and it didn't work very well with metal and metal. And that's my concern is that as new products come to market -- and I know we'll get to the, you know, the flexible designs later, but, you know, without having adequate clinical follow-up data on these patients, I just -- I maintain my concerns about these being the special controls.

DR. KELLY: Dr. Golish?

DR. GOLISH: If somebody from FDA can clarify, metal on metal is a Class III device subject to PMA without a long clinical track record and 20 years or more of success with respect to the most recent regulatory filings, not the historical ones.

MR. MELKERSON: Metal on metal were pre-amendment Class III in terms of the product and in terms of there was a separate action related to metal on metal.

DR. KELLY: So, I guess -- Dr. Lehman?

DR. LEHMAN: Ron Lehman.

Just a point of clarification maybe on that as well as total joint arthroplasty is meant to be a motion preservation type device, so the wear characteristics are going to be different than a rigid fixation type of system, whether it be a -- even a fusion for a hip versus a total joint replacement for a hip.

DR. KELLY: Yes, Ray?

DR. GOLISH: You know, I want to say I take Dr. Lyman's

critiques as very seriously since he has identified himself as a non-spinal expert but has clearly become a very astute consumer of the literature that's been presented. I think that that is important. I do want to point out that if the special controls listed -- anybody from the sponsor side who has run ISO 10993 biocompatibility testing, anybody who sat on ASTM panels, including Mr. Melkerson's 20 years of blood, sweat, and tears doing that, understands that, you know, this is really very extensive testing that in addition to the decades long track record of clinical studies, I think, is a good package of special controls that are understood and that have been reasonably well correlated to study the clinical outcomes.

And I do think that the clinical outcomes are essentially -- you know, what we really want to know, as Dr. Haines so astutely pointed out, is what's going to happen when we study -- do that study with an n of 1 for any one individual patient's condition on the countless specific issues for that patient. What we can know is what happens on the average marginal over lots of things related to technique, to implants, to radiographic correlates related to comorbidities. And I think that our literature shows that the two-stage syllogism from screws to fusion and fusion to outcomes is positive and that the special controls can support that continued success.

DR. KELLY: So, in consensus, these special controls are essentially adequate to ensure safety? Joe?

MR. O'BRIEN: I just couldn't honestly -- I still express the same

kind of concerns that Dr. Lyman has indicated. You know, and perhaps it's just my not knowing about labeling enough, but, you know, labeling as being the answer to all to these -- you know, but I just don't see it as being really a control enough factor for it, and my own -- notwithstanding, you know. And even -- you know, we're not looking at DSS now, but, you know, in those there is failure -- you know, prediction of failure from bench to outcome.

So, you know, I just -- I don't have that safety level myself because the indication here -- what we're talking about is the indication. With indication is going to come expansion, and with expansion is going to come different -- and that's my concern with it. So, you know, looking for postmarket surveillance is where I'm coming from still as I look -- an honest response to this as I look at it, so, again, maybe it's just my not understanding of labeling and the importance of the whole thing.

DR. KELLY: My understanding of labeling is it also includes indications, so I think that therefore would expand the labeling.

Am I correct, Mark, in that assumption?

MR. MELKERSON: If you were going to expand the indications beyond what's currently approved or cleared under 510(k), that would require a submission of a new 510(k), which would be assessed. Does it or does it not change the intended use, and does it still fall within that classification? If it does fall within the same intended use and you're technologically different, you could potentially need performance data, which

either could be bench, animal, or clinical data, depending on the difference of that technology.

And just following up on metal on metal, as I mentioned they were Class III pre-amendment 510(k)s. There were no special controls in place for those products. And we have recently gone out with a proposed order calling for PMAs, and we've received eight comments on that proposed order to call for PMAs for metal-on-metal hips, and we're currently analyzing those. And in the same context, anything identified as Class III still went through the 510(k) process, but we were applying the special controls used for the Class II indications when we were going through the clearance of those products.

DR. KELLY: So, Mr. O'Brien, it seems that there's reasonable checks and balances before gross expansion of usage.

Dr. Lyman?

DR. LYMAN: I think, you know, earlier we heard numbers of 500,000 a year and a million of these have been implanted, and I think we -- you know, as we keep the patient safety in mind, I'm concerned that, you know, laboratory testing alone may not be sufficient. We don't necessarily know what's going to happen when we put these into people, especially long term. And that may not be specific to these implants. These may be completely safe and effective implants, you know -- the points that you mentioned that these are for stability rather than motion.

But I think keeping that mind -- and, you know, we're entering an era where data is becoming increasingly accessible and increasingly easy to use, and we have computing power that we've never had before. So the barriers to doing this are relatively low compared to what they've been in the past, so whether or not it applies to these devices, I think we need to start to think about bringing the data sources that we have available to bear on these questions of long-term safety and effectiveness.

DR. KELLY: Yes, Dr. Golish?

DR. GOLISH: Yeah, that's an important point I'd like to comment on. I think that all the clinicians at the table would support me in saying that there's an extremely vigorous debate occurring within the realm of the practice of medicine on indications for use. This includes questions of DDD. It includes questions of safety. It includes payers, professional societies, surgeons, patients, and patient advocacy groups. And I think this gets to Dr. Haines' dividing line between the regulatory matters and the practice of medicine. And I would welcome your concerns in those forums because I think it would be a welcome, helpful voice as we all get more vocal about that.

And I think Dr. Lehman agrees as well, so, you know, our charge here today to consider the two-stage syllogism of fusion by means of screws and then outcomes by means of fusion is the central issue that I think this question addresses, but the safety concerns continue to be pivotal. I don't

personally feel that postmarket surveillance is the answer to that. I personally feel like a very vigorous reinvigorated debate about the practice of medicine that Dr. Haines has brought up is what's happening right now to address these important concerns.

DR. KELLY: I have a question for Mr. Melkerson is that obviously we have a clear sentiment that more clinical data may be necessary. I posed that question earlier. Maybe I'll just reformat it, that could that be listed under special control?

MR. MELKERSON: Clinical data can be a special control. Again, it's not a frequently used special control at this time, but it is an option.

DR. KELLY: Okay.

Yes, Dr. Haines?

DR. HAINES: So I would add that our charge is to recommend special controls that can adequately mitigate the risks. We have essentially apparently no experience with postmarket surveillance as a special control for a Class II like this, and generally postmarket surveillance has not been a terribly effective method of dealing with these issues, as we have seen with respect to the dynamic devices. So I just think we're not -- we would not be adding a special control that we know to be effective in accomplishing this.

DR. KELLY: Which to me sounds like we're treading into Class III territory. I mean we can only do what we can -- our charge is to state our recommendations. And if our recommendations are more clinical data, so be

it. It's up to the FDA to figure out -- to configure how to navigate those orders.

DR. HAINES: It's Dr. Haines again.

Well, I'll go back to my previous statement. I think that then we are treading very, very close to interfering with the practice of medicine and not what the FDA is charged to do under the definitions of the kind of valid scientific evidence that is appropriate to consider that we -- these special controls known to be effective for what they can do, and that data lead me to the conclusion that these controls are adequate.

DR. KELLY: Yes, Dr. Trier?

DR. TRIER: I would like to comment again on the postmarket surveillance issue and the comments that have recently been made. It's my perception that because of the postmarket surveillance that the Agency has done, that we now have the discussion today in this Panel meeting on the dynamic stabilization system. I would also suggest that the reason many of us were in attendance at the metal-on-metal panel meeting last fall was again because of the postmarket surveillance that the Agency actually does do.

Now, does that address your concerns for some kind of a randomized gold standard trial? Probably not. But I do think that there is -- there are processes within the Agency that does take account of those postmarket surveillance views of products after they are on the market. And the discussion today on dynamic stabilization systems I think is an example of

that.

DR. KELLY: Again, our charge is to answer the question, and I think we should do that in the best of our abilities.

DR. LYMAN: And I think if the post-approval folks at the FDA are doing that, then that's sufficient to me, if that answers the question. And I'm actually not a huge fan of surgical trials. I have reasons for that, but we won't get into it.

DR. KELLY: Well, with that in mind, I'd like to attempt to formulate an answer.

Mr. Melkerson, with respect to Question No. 3, it is the consensus of the Panel that on the whole the special controls are adequate to mitigate the risks to health for traditional, rigid pedicle screw systems. However, there's some concerns raised on again the definition of DDD. There is a concern about more precise labeling and accurate labeling. And there is clearly a concern for need for more clinical data.

Mr. Melkerson, is that a sufficient answer?

MR. MELKERSON: Let me ask for clarification. FDA's presentation was our assessment of the current available clinical data was that it provided a reasonable assurance. And part of this question -- and it relates back to are you agreeing with the special controls to help assure a reasonable assurance?

DR. KELLY: I think there's a -- this is a clear and sort of obvious

concern for more clinical data, so I think it -- the way the question is framed, I think we're going to have to reject that first supposition that there is a -- on the whole we agree with the controls, but the clinical data at this point is insufficient.

Yes, Dr. Pfeifer?

DR. PFEIFER: You know, again, first of all, to get the type of clean study that you want to get done, the prospective randomized controlled study, you're not going to do it in the United States. This is an impractical suggestion. I would refer you on grade 1 and 2 spondylolisthesis, that the best study we have available is out of Dartmouth. It's by Weinstein, et al. It's an NIH funded study. It clearly supports the indication of using these. There are other outcome studies that are either going to be available either through some of the -- I could quote you -- Zoher Ghogawala is pushing this now with the North American Spine and others.

So that we have to say what's reasonable and prudent for the FDA to do as opposed to what we'd like to have for an ideal. And I think as stands this is reasonable, this is reasonable and prudent. I may be wrong. I may have a disagreement, but for what you seem to be asking, I don't see practically how the FDA can do it.

DR. KELLY: I think that -- I just want to just take -- that, again, in the spirit of the question, though, we're not here to measure logistics or whether they can do this. We're here to really answer the question as

truthfully as honestly. And I'm hearing, you know, some honest commentary that we're not quite happy with the clinical data. So I think we just have to state the facts as they see it and let the FDA figure out the best resolution.

Yes? I'm sorry; I see that Dr. Lyman had his hand up first.

DR. LYMAN: I just want to make it clear I'm not actually asking for prospective randomized control trials to put this to bed. That's not at all what I'm asking for. I'm asking for evaluation of existing data sources in which these implants have been used in patients in which we can measure a lot of these outcomes relatively efficiently.

DR. PFEIFER: And if I could ask, how is that different than a review of the literature we just had?

DR. LYMAN: The literature as I understand it -- and, again, I had a lot of questions about length of follow-up and those sorts of things. That's where I think a lot of my concern comes in is whether or not the length of follow-up was equivalent and whether or not these rates really represent the truth or the best that we can assess it. And so, knowing how this works effectively in real world situations I think would be really useful information. I think that's something that is achievable.

DR. PFEIFER: That's why you rely on peer reviewed studies because most of the journals that are publishing in the United States are not going to accept a six-month follow-up. You know, it's the minimum standard is usually now about two years. So I don't see that there is not -- I think

there's enough data out there. Maybe I'm wrong.

DR. KELLY: I think that Dr. Lyman is expressing just perhaps some methodologic flaws that could be worked with with the present format. We don't have to recreate the wheel just to bring a different perspective on the way it was reported, the way the data was analyzed. Am I correct in that assumption?

DR. LYMAN: Right. From the presentation we had today, I didn't necessarily -- I didn't understand -- I mean I review for a lot of journals. I know what gets through and what doesn't, so I don't necessarily agree that just because peer review did it, it's a good research project. But the concern is that the way it was presented today, I couldn't assess whether or not these were safe and effective to my satisfaction. That doesn't mean they're not. Just that I'm not comfortable with that.

DR. KELLY: Dr. Rohr and then Dr. Golish.

DR. ROHR: Yeah, Bill Rohr.

I just wanted to say that the metal-on-metal issue is actually an aberration that has to do with an aberration of a way the regulatory system worked and pre-amendment devices, so I wouldn't use that as a good analogy. A better analogy would be the plates and screws that we use in fractures. And, in reality, these things in the spine are plates and screws like we use in the rest of the body except for they've been modified for the special anatomy around the spine. And in those plates and screws we use

ubiquitously throughout orthopedics, the special controls have worked extremely well.

We've gone through flexible, non-flexible, all these same issues. And now they've just been modified to the spine and to the issue that, you know, the fixation may be different, the indications may be different, but those are clinical questions. And I think we have a wealth of data even better than when we developed the first plates and screws for fracture fixation, to be perfectly honest. And I think that's a better analogy. And the special controls worked extremely well in those areas.

DR. KELLY: Yes, Dr. Golish?

DR. GOLISH: Is it fair to say that our mild reticence is exclusively related to DDD? And that, in fact, it's exclusively caused by the ambiguity historically in the definition of DDD, which may be irresolvable at this point? Is that a fair statement?

DR. KELLY: I think that's a good part of it. Am I correct in that assumption, Dr. Lyman?

DR. LYMAN: Yes, I would agree.

DR. KELLY: All right. Let's take another stab at this.

Yes, Joe?

MR. O'BRIEN: Just one further point that I would go on the record that I think is necessary for the FDA to look at, relative to this question, is the confusion -- and I agree with Dr. Haines where, you know, the

question and what we're being asked to, and the way you look at it, when you start talking about indications, it starts to get into the question of the practice of medicine. And I agree with Dr. -- it's absolutely essential to look at that issue as it relates to this because that is a concern that comes in here is it's not so much the specific about the device. It's the use of that device in this indication and what's going to happen with it that's there.

So I mean I -- in terms of my reticence, it's because now there's going to be 2 million patients, not 1 million to do that. And I -- you know, the scientific evidence -- I would agree with Dr. Lyman. I'm not an expert on that, but I don't get all that sense of the safety of it in that expansion. So that does get into another issue, and I realize that, so I'm willing to, you know, recognize my reticence and --

DR. KELLY: But don't let that reticence of walking the line interfere with your advocacy for our patients because everything we do there's consequences. I mean, the fact we label things in many respects restricts the practice of medicine. That's a very nebulous -- so I always have -- the spirit of our mission here today is to protect patients any way you see fit.

MR. O'BRIEN: But, specifically, I would say though for the FDA then, if you're going to ask a panel to make a decision and take a vote on a question about specific controls, and the literature at the FDA specifically addressed the clinical -- you know, postmarket surveillance and clinical data as being a special control that can be applied, there should be further

clarification under what circumstance is that appropriate or not do to that. It hasn't been -- it's rarely used. If that's the case, why? When is it appropriate and when is it not, so that subsequent future panels can have a much better definition as they go to answer the question.

DR. KELLY: Right. And that's for the FDA to decide, Joe.

MR. O'BRIEN: Right. I'm posing that for the FDA.

DR. KELLY: We just have to express our concerns and our inadequacies as we see the data presented.

Dr. Haines?

DR. HAINES: I would just say I think that the risk that this will result in a huge expansion is overestimated. I think that expansion has already occurred and that we're essentially bringing classification into accordance with reality.

DR. KELLY: I have to agree with that.

All right. Let's have another stab at this. Mr. Melkerson, with respect to Question No. 3, the Panel is in overall agreement that the special controls are reasonably adequate to mitigate the risks to health. However, there are remaining concerns about the definition of DDD, about precision of labeling, and there is a specially significant concern about the development and elaboration of clinical data.

Mr. Melkerson, is this an adequate response?

MR. MELKERSON: Actually, I'm going to kind of pursue the

labeling issue. Are there specific things that should be included in the labeling that aren't now? In other words, we've talked about indications. We've talked about patient selection. Are there other things that we're missing in the labeling? In other words, if we have specific concerns that the labeling is not adequate, are there things that we could add to the labeling to help in that matter?

DR. KELLY: We need to find out more about the current labeling. We know the indications we're posing. Anything else that Dr. Jean you can provide us with? Labeling?

Sure, Bill.

DR. ROHR: John, just let me -- Bill Rohr. I'm sorry. Let me clarify for the non-surgeons on the Panel, as a surgeon I've never read this so-called labeling, that package that comes in microprint that at my age I can't read anyway. But the fact of the matter is it controls --

DR. KELLY: Off the record.

DR. ROHR: -- it controls the way that the companies -- and I did work on that side of the aisle -- the way the companies are allowed to promote and market and teach, et cetera. So labeling has its effect on the spread of it. On my use as a surgeon, no, because first of all, I'm sterile and that thing is thrown out when I'm handed the device. So, you know, it doesn't affect me as much as the teaching and all that and how the company promotes it. So understand what the labeling really represents is not on the

surgeon. It really has to do more with the manufacturers.

DR. KELLY: You know, I have to say, Joe, looking at that, that's a pretty comprehensive list --

UNIDENTIFIED SPEAKER: I don't have any doubt --

DR. KELLY: Yeah, especially indications. I mean that's again -- Dr. Haines, we're getting into a nebulous area there. Indications for use, that's surgeon dependent, as he deems appropriate.

So Dr. Melkerson, have I filled your -- oh, yes.

DR. POTTER: Hollis Potter.

Just one concept about MR compatibility. These are all MR compatible in that they pose no harm to the patient when being scanned. The issue is more generation of artifact that diminishes our ability to perceive the soft tissue envelope around the implant in the presence of stainless steel. And that is a function of the protocol that's used as well as the advent of newer pulse sequences that have been developed. So to include this as MR compatibility I think puts -- is not really appropriate in this setting because these implants have been scanned for years, both the stainless steel as well as the titanium constructs. And the degree of artifact is a function of the magnetic moment, of course, with stainless steel being much higher than that of titanium. So that, I would question in this labeling.

MR. MELKERSON: Thank you. Just an added point, we clear specific indications for use. And the indications, although nebulous for DDD,

are indications that we've cleared for these products already, and we don't try to tread into the practice of medicine.

DR. KELLY: Very well. May we proceed to the next question, please?

MR. MELKERSON: Yes.

DR. KELLY: Thank you.

DR. KAVLOCK: FDA believes that the safety and effectiveness of dynamic stabilization systems, a subtype of pedicle screw spinal systems when intended as an adjunct to fusion, is not well established. FDA bases this determination on the lack of valid scientific evidence to support the safety and effectiveness for these uses. The potential risks to health associated with dynamic stabilization systems may not be the same as those identified for traditional, rigid pedicle screw spinal systems. Therefore, FDA does not believe that there is sufficient information to determine whether special controls can be established to assure the safety and effectiveness of dynamic stabilization systems as an adjunct to fusion. Please address the following questions. And I'll ask them -- each part separately.

Dynamic stabilization systems have different design features that allow bending or rotation while facilitating fusion. Components used to achieve this flexibility include polymer cords, moveable screw heads, and springs. Please discuss the technological features that fall under the scope of dynamic stabilization systems.

DR. KELLY: Dr. Lehman, do you want to tackle that one?

DR. LEHMAN: Ron Lehman.

Yeah, but I think this is certainly an apples to oranges comparison I think of what we're talking about today. I think the preponderance of the literature with the rigid screw systems is much different than the dynamic systems, and the technical features obviously are different. We talk about dynamic systems that involve pedicle screw instrumentation are a little bit different in that these are implants. And even in the pediatric population, we have growing rod type scenarios where we're trying to obtain partial fusion at certain levels to act as a base or a platform, and then with either mobile longitudinal connectors, screw heads, set screws to allow for longitudinal growth. That could be a scenario where this is employed.

Certain other ones where even for grade 3 and 4 spondylolisthesis where we have a high-grade spondy that has been reduced and fused at the essentially index level, there are occasions when adjacent to that or super adjacent to that, so meaning above that fusion level, where a type of polymer cord or a relatively mobile or dynamic device can be employed to obtain additional fixation, which isn't necessarily meant or intended for fusion, but for additional stability without fusion, can be employed.

But, once again, I think the preponderance of the level of

evidence provided today by the FDA is not as formidable as it is for the rigid screw constructs.

DR. KELLY: So we have to answer the question of what features particularly, Dr. Lehman, would qualify something as a dynamic system?

DR. LEHMAN: I think in my mind, what qualifies as a dynamic system is anything other than an indication for immediate stability in a rigid type construct. So to break it down in very basic terms, for me, am I'm trying to not allow any motion at this segment with a spinal type system, or I am intending -- or am I intending either through longitudinal member, screw head interaction, or any type of dynamization whatsoever for whatever intended purpose. So to me it's do I intend to provide immediate rigid stability, or do I not intend to do that?

DR. KELLY: Anyone have any dissenting opinions? It works with me. What do you think, Steve? Both, I'm sorry, Dr. Lyman and Dr. Haines? Dr. Haines, the clinician first.

DR. HAINES: Yeah, that seems a reasonable definition.

DR. KELLY: Dr. Lyman --

DR. LYMAN: I'm certainly deferring to the surgeons on this one.

DR. KELLY: -- as the scientist here?

DR. LYMAN: I'm deferring to the surgeons on this.

DR. KELLY: Okay. No stats here too, so that's good.

Dr. Graf, clinician input? Dr. Do?

DR. GRAF: I think that's a very good definition, because as we've seen, some of these systems are I think purposely put through for an indication of fusion, which are not intended for such. And I think that's a good definition for immediate stability, and I think that's appropriate.

DR. KELLY: Dr. Do, any comments?

DR. DO: No. I agree with Dr. Lehman.

DR. KELLY: Okay. Very well.

I think, Mr. Melkerson with respect to Question 4a, it is the Panel's considered opinion that the features of the construct that are intended for anything other than rigid fixation stability would fall into the realm of dynamic stabilization.

Mr. Melkerson, is this an adequate response?

MR. MELKERSON: Yes.

DR. KELLY: Okay. The second part of the question, please?

DR. KAVLOCK: Actually three parts.

Part b is please state whether there are any differences in the risks to health for dynamic stabilization systems as compared to traditional, rigid pedicle screw systems, and specifically identify any risks to health that have not been discussed in the response to Question 1.

DR. KELLY: Could we see a slide of those risks that were already mentioned, please?

Anyone wish to add -- yes, Dr. Rohr.

DR. ROHR: Yeah, because these systems provide motion, there is a definite risk to the production of wear particles. And, of course, this is in close proximity to the spine of which we have little or no information. So I think you have to add these wear products brings back our metal-on-metal hips. We have to revisit that when we have now systems that are designed to have motion and moving elements within them adjacent to the spine. So I think you have to add wear products and possible toxicity from those, which is again not just a material issue but also a submicron particle issue and cellular response.

DR. KELLY: Very well.

Dr. Lehman?

DR. LEHMAN: Ron Lehman.

I think one of the -- three of the issues I think that came out during the FDA's presentation today when they were looking at comparing dynamic stabilization systems to rigid were the following: so additional procedures 46.9%, device breakage 59.8%, and pain 27.2%. These were all statistically significantly higher than the other systems. So some of these are certainly encompassed with this device breakage, implant loosening, and that type of thing, but obviously pain is not necessarily included in there on that list as I see it. And, you know, additional procedures, there's revision surgery, but these particular three things were significantly statistically different than

the rigid ones in the presentation that the FDA made.

DR. KELLY: So you're okay, Ron, with the -- this is an inclusive -- that would cover all the concerns you just mentioned?

DR. LEHMAN: Correct. It says back or leg pain, so pain I guess as an overall conglomerate of pain.

DR. KELLY: Ms. Bechtold, do you have a comment?

MS. BECHTOLD: Yes, Stephanie Bechtold.

Just to clarify, the three adverse events just mentioned, those came from the MAUDE search. We did not determine statistical significance for those numbers. We just highlighted those as those events had a higher proportion of those types of events occurring within that product code for the NKB dynamic stabilization systems. So it was flagged as something that might be an increased risk, but there is no statistical significance to those numbers.

DR. KELLY: Any comments?

Can I have the question again, just so I can read it with some semblance of intelligence?

So, Mr. Melkerson, it is the opinion of the Panel that the risks stated in Question 1 in essence apply to the dynamic stabilization system with the addition of wear particle consequences.

Mr. Melkerson, is this a reasonable answer?

MR. MELKERSON: Yes.

DR. KELLY: Thank you.

DR. KAVLOCK: Part c. Do you agree that the available valid scientific evidence is not adequate to support the safety and effectiveness of dynamic stabilization systems intended as an adjunct to fusion? If you do not agree, please explain by identifying and discussing the following:

the valid scientific evidence available in support of a reasonable assurance of safety and effectiveness of dynamic stabilization systems when intended as an adjunct to fusion, and

the special controls that you believe would be sufficient to mitigate the risks to health and provide a reasonable assurance of safety and effectiveness of dynamic stabilization systems intended as an adjunct to fusion.

DR. KELLY: Is the answer of the Panel I think -- I'm assuming most of us are in consensus that the evidence is not valid to support this as an adjunct to fusion. I think Dr. Graf has made that pretty clear.

Any dissenting comments? If so, what are the special controls we believe to be sufficient?

What would you like to see, Dr. Lyman, to ensure that these are safe?

DR. LYMAN: Sorry. If I understand the question, you only answer those if you don't agree with the statement. I think we're agreeing with the statement.

DR. KELLY: Okay. Well, I think they want us to elaborate on the controls that would be sufficient to mitigate the risks, but --

MR. MELKERSON: Dr. Lyman is correct. If you can get past there's sufficient available scientific evidence, then if you don't agree, then explain why.

DR. KELLY: I see. Okay. So it is the Panel's consensus with regard to Question No. 4, Mr. Melkerson, that we are in agreement that the available evidence is not adequate to support the safety and effectiveness of DSSs intended as an adjunct to fusion.

Is this an adequate response?

MR. MELKERSON: Yes.

DR. KELLY: Thank you, Dr. Lyman. I got confused with those double negatives there.

Okay. Can we have the next question, please? That's almost -- I remember seeing George Carlin non-inflammable.

DR. KAVLOCK: Question 5. The following question relates to the Class III eligibility of pedicle screw spinal systems.

Section 513 of the Food, Drug, and Cosmetic Act states that a device should be Class III if:

Insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of its safety and effectiveness or that application of special controls would 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.

The FDA believes that traditional, rigid pedicle screw spinal systems could be eligible for classification as a Class III device because they are permanent implants. However, the FDA believes that sufficient information exists to develop special controls that would provide reasonable assurance of safety and effectiveness.

Do you recommend Class II or Class III for traditional, rigid pedicle screw spinal systems as an adjunct to fusion for the treatment of degenerative disc disease and spondylolisthesis other than either severe spondylolisthesis (grades 3 and 4) at L5-S1, or degenerative spondylolisthesis with objective evidence of neurologic impairment? Please provide a rationale for your final classification recommendation, taking into account the available scientific evidence, the special controls proposed in Question 3, and the criteria listed above for placing a device into Class III.

DR. KELLY: Well, let's try to make it easier. Are we in consensus that for the other spondys, we're in agreement that this is a reasonable Class II recommendation?

So let's get to the Pandora's box, the DDD. What could we

safely say what our recommendations, in essence, that we'd like to see further elaboration of the definition of DDD, of course. Anything else -- I'm picking on Dr. Lyman, but -- yes, Dr. Pfeifer?

DR. PFEIFER: Okay. Now, in English, I think using the rigid pedicle screw device as an adjunct to obtain a solid fusion if felt indicated in the treatment of degenerative disc disease. The fusion felt indicated in the treatment of degenerative disc disease makes it a level II device. That doesn't answer -- the question is does it help the fusion? The answer is yes. Is fusion the correct treatment for degenerative disc disease becomes a question for another day.

So by keeping it to adjunct for obtaining a solid fusion in degenerative disc disease gets the FDA a clarification on whether it should be an -- I'm sorry, level II or level III device, but doesn't get us into the quagmire of trying to answer what degenerative disc disease is.

DR. KELLY: Thank you.

Dr. Golish?

DR. GOLISH: Yeah, I agree completely with Dr. Pfeifer. The question of the practice of medicine, there's a very vigorous debate going on outside this room all the time.

DR. KELLY: For the purposes of progression, would it be reasonable to say that for indications for DDD as we understand it, but we have concerns about the true definition? Would that be a reasonable

statement? Anyone comment upon that?

Dr. Haines?

DR. HAINES: Steve Haines. I like the formulation because it does get us away from that conversation about the definition of degenerative disc disease, and it focuses on the actual reason for considering the use of these systems in degenerative disc disease, which is if you -- if the physician feels a fusion is a necessary part of the treatment, then we have reasonable data to assure safety and efficacy.

DR. KELLY: Okay. You're squirming, Carl. Are you okay with this?

DR. GRAF: No, that satisfies my concern and my need for clarification of the definition of degenerative disc disease, and I think that's nicely stated.

DR. KELLY: So let's try this. Mr. Melkerson, it's the Panel's recommendation or consensus that we recommend Class II status for traditional, rigid pedicle screw systems as an adjunct to fusion for the treatment of DDD as we understand it, and spondylolisthesis other than severe grades 3 or 4, or degenerative spondy with objective evidence of neurologic impairment. However, the Panel has some concerns on the true definition and elaboration of precisely DDD.

Is that an adequate response, Mr. Melkerson?

MR. MELKERSON: That's an adequate response, yes.

DR. KELLY: Thank you. The Hail Marys worked.

Okay. The last envelope, please.

DR. KAVLOCK: Similarly, the FDA believes that dynamic stabilization systems could be eligible for classification as a Class III device because they are permanent implants. In addition, the FDA believes that insufficient information exists to determine if general controls and special controls would provide reasonable assurance of safety and effectiveness.

Do you recommend Class II or Class III for dynamic stabilization systems when intended as an adjunct to fusion for any indications? Please provide a rationale for your final classification recommendation, taking into account the available scientific evidence, special controls you proposed in Question 4 (if any), and the criteria listed above for placing a device into Class III.

DR. KELLY: So I'm going to take the liberty of using Dr. Lehman's, I thought, ingenious definition for indications when the implant is used for intentions other than immediate stability would thereby be qualified as DSS. And I think we're in consensus that there's not sufficient data to recommend its safety. Any dissenters to that comment?

Consumer reps? Patient Reps? How about Bill Rohr, the world's smartest man? Bill, any other comments?

DR. ROHR: I think Dr. Lehman hit a homerun with his definition, and I think we've been shown nothing that would say it should be

anything other than a Class III device.

DR. KELLY: Well stated.

Mr. Melkerson, it is the consensus of the Panel, given our previous definition of dynamic constructs, that when applied to this question, the Panel is in consensus that there is unsatisfactory data to ensure the safety and effectiveness of DSS, and thereby it should be qualified as a Class III device.

Mr. Melkerson, is this a reasonable response?

MR. MELKERSON: Yes. One clarification of the question was using the criteria that we're -- the lead in, which is, is it due to probable risk to injury, lack of data. Just clarify that.

DR. KELLY: I would say it's both. I think the answer would be all of the above, sir.

MR. MELKERSON: So if the device presents a potential unreasonable risk to injury, it's not -- is it life-sustaining and life-supporting, or for which there is a substantial importance in preventing impairment of human health, using those criteria at the beginning of 5.

DR. KELLY: I would think the safety and effectiveness would apply. There's no life threatening -- could you show us the slide of Dr. Kavlock of -- so I can read this? Is it up there?

DR. KAVLOCK: It's up.

DR. KELLY: Okay.

DR. KAVLOCK: So the first part is insufficient information exists to determine that general controls are sufficient to provide a reasonable assurance of its safety and effectiveness, or that the application of special controls would provide such assurance. And then part 2 is the life-supporting, life-sustaining, or if the device presents an unreasonable risk of illness or injury.

DR. KELLY: Dr. Golish? A question?

DR. GOLISH: Yeah, we spent a lot of time looking at the flowchart yesterday, if anybody would find that helpful.

DR. KELLY: The flowchart on I think it's page 9 of Dr. Shulman's handout. But, essentially, I think we can safely say that it's the Panel's consensus that general controls are insufficient and the device is non-life-supporting and life-sustaining. Therefore, it is the Panel's opinion that it should be classified as Class III.

Mr. Melkerson, is this a reasonable response?

MR. MELKERSON: We can use it.

DR. KELLY: You'd never make it as a life coach, Mark.

(Laughter.)

DR. KELLY: Now, the last envelope, please.

DR. KAVLOCK: Following this Panel meeting, the FDA will work to update the existing pedicle screw spinal system regulation, 21 C.F.R. 888.3070, based on the Panel's recommendation for classification. Please

address the following questions:

a) The current regulation describes pedicle screw spinal systems used as an adjunct to fusion as intended for "skeletally mature patients" for the Class II indications for use, while the regulation is silent with respect to skeletal maturity in the Class III indications for use. However, FDA has cleared numerous pedicle screw spinal systems dating back to 1998 for general pediatric use, as well as for specific pediatric indications for use (e.g., "adolescent idiopathic scoliosis," "spondylolisthesis/spondylolysis and fractures caused by tumor and/or trauma"), that incorporate the skeletally immature patient population. Consequently, FDA proposes to remove the "skeletally mature" terminology from the indications for use for this device type for either the Class II or the current/existing Class III indications for use. Please comment on whether you agree with this proposal, or whether you believe that any other terminology should be used in lieu of "skeletally mature," if any.

DR. KELLY: Let's just reframe that. Does anyone have any objections to the use of this technology in immature spine? Clinicians?

Patient advocates, any concerns about using this technology in growing spines? Dr. Lyman?

DR. LYMAN: Just a point of clarification on the previous approvals in pediatric use, you know, you have the list here. Were those -- did those require PMA, or were those 510(k)?

MR. MELKERSON: Those were all 510(k).

DR. LYMAN: So we did not have clinical data demonstrating safety and effectiveness for use in kids, right?

DR. KAVLOCK: Clinical data was provided in support of the 510(k) application, but it was cleared through the 510(k) regulatory process, thus making it Class II, but it did have clinical data to support safety and effectiveness.

DR. KELLY: Okay. And we didn't see any data today on safety or effectiveness in pediatrics. None of the presentations we saw addressed that issue at all, so I feel blind in supporting this.

DR. KELLY: Dr. Haines?

DR. HAINES: I think the perspective -- my perspective here would be that denying children the benefits of this device would be a very bad thing to do in the absence of data demonstrating that it was different in a major way.

DR. KELLY: Dr. Lyman's perspective is like where's the beef? So I can see this -- but that's why we're all here. We have to develop a consensus. So if the spirit of the Panel is that there's significant gain and withholding this technology would be, in essence, harmful to others, would it be -- yes, Dr. Lehman?

DR. LEHMAN: Ron Lehman.

Yeah, I think maybe what Dr. Lyman's alluding to is none was

presented today, but certainly I think the spine surgeons on the Panel, I would suppose there is a preponderance of evidence in the literature supporting the use for spondylolisthesis and whatnot on skeletally immature patients.

DR. LYMAN: One more question then to the surgeons. You had mentioned earlier that, you know, sometimes it sounded like even in adults, these screws can end up places they're not supposed to go and that sort of thing. Is that a higher risk in children because of smaller spines?

DR. LEHMAN: Ron Lehman again.

In theory, yes. Like anything else, if it's smaller, it's going to be more difficult to place the screw. But, once again, this is surgeon technique and not necessarily -- not as much of related to the implant itself as to the person doing the implanting, if that makes sense.

DR. KELLY: Okay. Dr. Do?

DR. DO: Yeah, I agree with Dr. Lyman in the skeletally immature patient population. My concern, number one, is that we don't have -- or we're not -- the data is not shared with us today. I'm sure it's out there, and I would advise the FDA to do a literature search on skeletally immature patients. And number two is I'm concerned about the reoperation as these kids I imagine would grow and would need replacement hardware.

DR. KELLY: Mark had some clarification.

MR. MELKERSON: In our systematic review, the age range was

15 to -- and above, but I don't know about our targeted review.

DR. DEVLIN: Vincent Devlin.

In the targeted review, this was the adult population, but in the Executive Summary, which was provided to all of the Panel members, there is data on the pediatric population contained there.

DR. KELLY: Dr. Golish?

DR. GOLISH: To speak to Dr. Haines' point about the patient potentially at risk of being left off this label, think about a 16-year-old with a grade 1, now grade 2, isthmic spondylolisthesis become newly symptomatic through extension type exercises, sports. That's a very real possibility. Some of those may very well have been captured by the spondylolisthesis papers, isthmic spondylolisthesis.

DR. KELLY: Yes, Ron?

DR. JEAN: Hi. Ronald Jean.

Just to clarify, with this question we are asking you whether we need that terminology within the classification. If you recall, earlier on in our presentation, we identified that we had already deemed that skeletally immature patients were within the scope of the classification. We've already cleared 510(k)s, some with supporting clinical data, for some of the Class II type indications, and it's explicit within our current Class II indications for use section. It is not present in the Class III indications for use section, DDD and other spondy.

So we are simply asking whether you believe it's necessary to have any description of skeletally mature or immature within the regulatory definition. Thank you.

DR. KELLY: Dr. Pfeifer?

DR. PFEIFER: The intuitive question somebody seemed to ask before was if you do a fusion and the kid grows, you're going to need to do another fusion. John Hall answered that question years ago where basically kids with severe curves do better if you fuse them and grow taller than if you wait. And they don't necessarily need to go further. And there's data out there and papers out there. You do a much better job if you have multipoint fixation in a kid straightening out a curve than if you don't. And don't confuse growing rods, which are a separate issue, with again adjunct to a fusion.

DR. KELLY: I don't have any -- myself any objections to running that terminology. Anyone dissent with that opinion?

Mr. Melkerson, it is the Panel's opinion that the terminology "skeletally mature" can be safely removed from the indications for use for this device for either Class II or currently existing Class III indications.

Is that an adequate response?

MR. MELKERSON: Yes.

DR. KELLY: Thank you.

Dr. Kavlock? Hang in there. You're almost finished, young lady.

DR. KAVLOCK: There are various interpretations and definitions

in the medical community related to degenerative disc disease.

FDA's "Guidance Document for the Preparation of IDEs for Spinal Systems," issued on January 13, 2000, defines lumbar DDD as "back and/or radicular pain with degeneration of the disc as confirmed by patient history, physical examination, and radiographic studies with 1 or more of the following factors (as measured radiographically, either by CT, MRI, plain film, myelography, discography, etc.):

- instability as defined by 3 mm of translation or 5° angulation;
- osteophyte formation of facet joints or vertebral endplates;
- decreased disc height, on average by > 2 mm, but dependent upon the spinal level;
- scarring/thickening of ligamentum flavum, annulus fibrosis, or facet joint capsule;
- herniated nucleus pulposus;
- facet joint degeneration changes; and/or
- vacuum phenomenon.

In addition, FDA-approved PMAs were based on IDE studies that enrolled patient populations that were primarily diagnosed with DDD but also included patients with grade 1 degenerative spondylolisthesis and subjects with a history of prior spinal procedures, including discectomy,

laminectomy, laminotomy, or nucleolysis at the target spinal level.

As the regulatory definitions of DDD described above include posterior elements beyond the spinal disc that resides in the anterior column of the spine, would degenerative spine pathology (or DSP) more aptly describe these findings? Please comment on whether you agree with this new terminology, whether DDD is adequate to describe the conditions above, or whether you believe that other terminology would be more appropriate.

DR. KELLY: Dr. Golish?

DR. GOLISH: With the definitions that we've been employing and that have been suggested today, I think we've managed to achieve an implicit operational definition that works for the question of whether to down-classify rigid pedicle screw systems to Class II. With respect to other IDE trials and PMAs, I would strongly encourage FDA to consider those on a case-by-case basis even more carefully with more scrutiny. People here on this Panel today have sat on other panels with big, expensive, long-term IDE studies and reviewed them, and it was clear that in fact the definition of DDD with other entities such as spondylolisthesis was conflated.

And I object to the language chosen here of the patients were primarily diagnosed with DDD, but also included other patients. In fact, sponsors were questioned carefully about what were the different enrollments. So take, for example, a group that is 80% stenosis with spondylolisthesis and a group that's 20% DDD, meaning black disc disease in

the most concise description. This patient group is going to have a big effect size. This patient group will have maybe a smaller effect size. When you put them all together, you still get a pretty good effect size.

When you leave your clinical trial and go out into the community, in fact about 20% of people fall into this group, 80% fall into this group. And so now the device has potentially captured this giant universe of patients that didn't necessarily represent well in the trial. So I think that FDA needs to sharpen this definition, sharpen the inclusion criteria for future IDE trials, and I don't think we can completely resolve this big a question today.

DR. KELLY: How do people feel about the new definition of degenerative spine pathology? Is it going to help or hurt us?

Dr. Graf?

DR. GRAF: It's just going to further the confusion. I don't think it's going to clarify anything. It's just going to rename it.

DR. KELLY: So the big issue is -- well, how do you best suggest we resolve, Dr. Graf, this uncertainty or this obfuscation of what in your mind constitutes DDD? Suggestions?

DR. GRAF: Carl Graf, again.

In general, I do agree with the terminology of degenerative spine pathology. I really think it's outside of the scope of the discussion today with pedicle screws rotation to define specifically what the FDA should use as a whole for, as we mentioned, other studies as inclusive in that. I think

that that's a big challenge for this Panel.

DR. KELLY: Let's go back to the first question. Do we all think that DDD the term is sufficient alone as it stands?

Dr. Haines?

DR. HAINES: I wouldn't make it any more inclusive than it is. The problem is it's too inclusive and that you end up studying such a disparate group of patients that you can't come up with a specific indication for a specific device. So I wouldn't make it bigger.

DR. KELLY: Make what bigger? The term includes everything. You would define -- you would add to that list that was so --

DR. HAINES: No. I would not add to the list. I actually think the problem is that the existing definition is too broad and vague.

DR. KELLY: Yes, Dr. Rohr?

DR. ROHR: Let me suggest that we suggest to the Agency that they follow the skillful guidance of Drs. Pfeifer and Lehman here today, and instead of incorporating in your, you know, IDE trials and the term DDD, use the very nice guidance they've given as to how to restrict the use of it. In other words, where for instance a fusion is indicated and this is an adjunct. So leave out that term and -- because I think Dr. Pfeifer has explained it. I mean almost every journal article that uses this term, every panel that uses this term all admit they can't define it. So let's get around it and stick more to the specific indications. The kind of guidance they've given today I think is

the answer.

DR. KELLY: But what are you going to call it, though, Bill? I mean would it be just back pain? I mean, you know, there has to be some label, I think.

DR. ROHR: I don't think so. I think when you're creating indications for use, they've given very clear indications of how to break down these definitions. And instead of using a disease as an indication, use the guidance they've given you that when -- you're trying to get a fusion and this is an adjunct to a fusion, it doesn't matter what disease it's for, probably, I think in general.

DR. KELLY: Dr. Pfeifer?

DR. PFEIFER: I worry about the degenerative spinal pathology bringing up what I just commented before in the open session. In degenerative spinal pathology, you can use a fusion for a herniated disc, a brand new herniated disc. Now, when you talk to a spine surgeon about degenerative disc disease independent of anything else, I usually excluded the spondylos and what have you. It meant to me a purely degenerative disc -- whatever you use as that criteria -- with back pain, as opposed to radiculopathy, as opposed to spondylolisthesis as a special class or extension of this degeneration.

I actually like the term degenerative disc disease without any other mechanical -- I'm saying I like it as specifically meaning no

spondylolisthesis, no this, no that, the purely degenerative disc. And keep your studies clean and use what I consider the restrictive definition of degenerative disc, which is a non -- unstable -- and, again, the whole instability question because to a spine surgeon, instability means they have pain when they move. Well, that's -- you know.

But I think the FDA can keep what it's got and just tighten up the fact that you're going to a study on degenerative discs, you're going to exclude the patients with the grade 1 and grade 2 spondylolisthesis, the fractures, the this, the that, and then you'll get what you want, which is do you want to do a fusion for a purely degenerative disc and keep it restrictive to that? But I speak against going to degenerative spinal pathology. It's like saying we're going to have an ICD-10 classification of one code.

DR. KELLY: Okay. You had a comment, Dr. Lehman?

DR. LEHMAN: I mean I think the term degenerative spinal pathology is a little bit obviously more inclusive. I think the DDD term for most spine surgeons, and even for non-surgeons, is more of a negative impicator. So you hear DDD, I think you think more what Dr Pfeifer said, someone with back pain with no radiculopathy and you're -- you know, it's very much a clinical dilemma.

And so, I think if you say degenerative spinal pathology or degenerative conditions of the spine, which you would like to achieve a fusion based upon your clinical effectiveness and what you think is best for

the patient, as a qualifying statement it may be a little bit better than labeling things, if that makes sense, for indicated reasons -- indicated clinical reasons.

DR. KELLY: Who on the Panel would favor the adoption of DSP versus DDD? Okay, so we have one.

So if we're going to accept DDD, would we include in a recommendation to the FDA just the further refinement? You know, the funny thing is we all know the patient that they're alluding to, but we just can't articulate it any better.

Yes, Dr. Graf?

DR. GRAF: Well, first off, I mean if we're going to go down the road of trying to define this, then we should -- as an indication, we should have something in there about symptomatic degenerative disc disease.

DR. KELLY: They mention -- low back pain. I believe Dr. -- maybe showed that slide before, but it was low back pain and non-radicular. I think they include that as well. But obviously it clearly has to be symptomatic.

Any other further refinements we can use to the term DDD?

So we're going to recommend that perhaps as it stands, we can adopt -- we can continue the adoption of that term, but we have concerns about refining it more specifically to apply to certain patient subsets. Would that be a reasonable comment?

Mr. Melkerson, with respect to Question No. 6 (i), the Panel is

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in agreement that there is no need to adopt the term DSP, that we are comfortable with the continued use of the term DDD. However, we have some concerns about the precise definition of what this constitutes and would like to see further refinements of the applicability of this term.

Mr. Melkerson, is this a reasonable answer?

MR. MELKERSON: I believe we'll take it as what it is, but in terms of our moving forward, we will probably go out with a proposal within a proposed order trying to take your comments into consideration.

DR. KELLY: Thank you.

DR. KAVLOCK: So part (ii) of that question is related to the question above, FDA's "Guidance Document for Industry and FDA Staff: Spinal Systems 510(k)s" issued on May 3rd, 2004, defines DDD as neck (cervical systems) or back (for non-cervical systems), pain "of discogenic origin with degeneration of the disc confirmed by history and radiographic studies." Please comment on the adequacy of this regulatory definition, or whether you believe that additional details not captured in this definition should be described to define DDD, such as the need to distinguish between symptomatic and asymptomatic spinal degeneration, as well as the need to identify clinically relevant subgroups in the DDD or DSP population.

DR. KELLY: Okay. Let's tackle that one. Anyone have conviction against stratifying this for neck and back?

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Yes, Dr. Haines?

DR. HAINES: Haines.

Well, we just discussed that symptomatic is probably important. I don't think we want to be out there studying these devices for completely asymptomatic patients.

DR. KELLY: Yes, Dr. Rohr?

DR. ROHR: I think part of the problem is we're trying to call something a disease that's probably not a disease. It's a condition for which there are many etiologies. And the problem is we don't have a marker that says you do or don't have it. So I don't think there's a way, Mark, to give the Agency any better clear indication because again it's probably a wide spectrum of conditions that all lead to something that radiologists and people have put some terms on and that we try to struggle with. But so long as there's no marker for it, I mean all you can do is exclude those diseases which do have a marker, you know, rheumatoid arthritis of the spine, et cetera.

So I think we can't give you a concise definition when we don't actually have a singular disease and certainly one that doesn't have a marker for us to define yea or nay.

DR. KELLY: Dr. Golish?

DR. GOLISH: The question of is there a biomarker for discogenic origin of pain with DDD is a complex one. Dr. Potter has published on T1 rho signals and other MR signals. I've published on molecular

biomarkers. Various people have advocated provocative discography or anesthetic discography. Various people have criticized that technology. And, so, there's no simple way to encapsulate that into a is there or is there not a marker. But the question of being able to diagnose the origin of discogenic pain is essential.

DR. KELLY: Yes, Mr. O'Brien?

MR. O'BRIEN: I just want to point out I was confused by the question because the definition, the current definition already assumes that it's symptomatic because it defines it as being cervical back pain. So to be asked whether or not we want to differentiate was a confusing question.

DR. KELLY: I agree with that, that it is included definitions.

You have a comment, Dr. Potter?

DR. POTTER: No. I think we can provide objective evidence of disc desiccation, loss of water content, that is there that is a marker of degenerative disc disease. But it is present and well documented in both symptomatic and asymptomatic cohorts. So I think that the definition as it stands, as long as the clinicians are confident that the pain syndrome associated with disc disease is different than that from radicular pain -- and I think it is -- as it stands with degeneration of the disc confirmed by history and radiographic -- like I would say, imaging studies because then obviously MR is not radiographic, so I would say imaging studies -- is appropriate.

DR. KELLY: But I think -- isn't MR or other imaging that includes

-- the definition Dr. Kavlock provided earlier I think was x-ray and MR, I believe, but I take your point.

Joe? You had a question? Mr. O'Brien?

MR. O'BRIEN: No --

DR. KELLY: All right. So we are in agreement that this is essentially going to fly, there's no issue with the neck or back, and that we want to make sure that the inclusion of symptoms is emphasized.

Mr. Melkerson, with respect to Question 6 (ii), it is the Panel's considered opinion that the definition hereto provided is sufficient. There are some concerns that then inclusion of symptoms and refinement of imaging definitions be included. Is this a reasonable response?

MR. MELKERSON: Yes, and I thank you for dealing with some of the questions, difficult questions we've been dealing with since the reclassification back in the '90s.

DR. KELLY: You're welcome.

DR. KAVLOCK: Part c. 21 C.F.R. 888.3070(b)(1) currently contains the requirement for a warning and a precaution in the labeling for the Class II indications.

Part (i) of this question is that 21 C.F.R. 888.3070(b)(1) currently requires the following warning. "Warning: The safety and effectiveness of pedicle screw spinal systems have been established only for spinal conditions with significant mechanical instability or deformity requiring

fusion with instrumentation. These conditions are significant mechanical instability or deformity of the thoracic, lumbar, and sacral spine secondary to severe spondylolisthesis (grades 3 and 4) of the L5-S1 vertebra, degenerative spondylolisthesis with objective evidence of neurologic impairment, fracture, dislocation, scoliosis, kyphosis, spinal tumor, and failed previous fusion (or pseudoarthrosis). The safety and effectiveness of these devices for any other conditions are unknown." Given the findings presented to this Panel, FDA believes this warning is no longer relevant.

Please comment on whether or not the removal of this warning is warranted, given that there is additional clinical data available since the creation of the original pedicle screw classification regulation.

DR. KELLY: Dr. Graf?

DR. GRAF: I mean given our discussions and our recommendations as a whole, this would no longer be relevant as proposed.

DR. KELLY: Dr. Lyman?

DR. LYMAN: If I can just ask one question about this? Couldn't this language simply be refined to include the things that we're now saying there is adequate safety and effectiveness? Because presumably there could be other indications that aren't covered yet, in the realm of practice, right? So it seems like maybe a modification of this might be worthwhile.

DR. KELLY: Mr. Melkerson?

MR. MELKERSON: Typically warnings are for indications where

there is no information. The labeling in the indications for use typically identify what has been cleared for that product, so warnings are usually intended for things we didn't have sufficient information at the time.

DR. KELLY: So it looks like -- it looks to me, my reading is that all these indications have some data available, so I'm cool with removing this.

Dr. Golish?

DR. GOLISH: I think I agree that our affirmative answers to Questions 2a and b about safety, efficacy, and risk/benefit ratio sort of imply that we don't think that this is any longer required.

DR. KELLY: Yes, Dr. Pfeifer?

DR. PFEIFER: Dr. Pfeifer.

On the other hand, I would almost say this clearly states what we think these ought to be used for, meaning we had this whole issue -- I would almost say why not keep it and change the severe spondylolisthesis grade 3 and 4 to, you know, any spondylolisthesis? And it clearly states it's mechanical instability, however you want to define it, or deformity related to these conditions. And that -- you know, I don't know whether it needs to be a warning. It's almost this is what we want it used for. Am I missing something here is what I'm trying to get to? Because this clearly says it's mechanical instability. It's not just a degenerative disc.

And, you know, should it be somewhere in indications rather than the warning? And should the only change be getting rid of the grade 3

and 4 spondylolisthesis and just put the word spondylolisthesis? Am I reading it wrong? Again, I'm an engineer, guys, so, you know, by training.

DR. KELLY: I don't know. I think you may be opening Pandora's box to say all spondy. I think as it reads right now -- I'm okay with that, but I'd like to hear the Panel members weigh in. I don't think it's a major concern on my part.

Mr. O'Brien?

MR. O'BRIEN: Along the same lines, I guess the only thing that stuck out to me is mechanical instability or deformity requiring fusion. And I thought we -- that is the definition and a warning. It's only to be used with fusion.

DR. KELLY: I mean, if you read that, Bernard, it's like other spondys would apply and DDD; that's the spirit of this question, I think.

Yes?

DR. PFEIFER: Well, you know, but it -- that's what you use it for, you know, spondylolisthesis. I think it's one of the better indications for it, no matter what the grade. And I just think this puts it into what we think it works for and takes away the issue of using it for purely degenerative discs without instability.

DR. KELLY: Well, as I read this question, it's just really saying that there should be a warning for grades 1 and 2 and for DDD. And by admitting this warning, you're allowing the usage of those other two

indications so -- am I not reading this properly?

DR. PFEIFER: Well, we already said we were making it a Class II device for grades 1 and 2 spondylolisthesis.

DR. KELLY: So, therefore, I think --

DR. PFEIFER: So if you take out the restrictive spondylolisthesis thing here -- in other words, I would probably say secondary to spondylolisthesis, degenerative spondylolisthesis with objective evidence, and then keep going. If you want to put symptomatic spondylolisthesis in there, you can do that too.

DR. KELLY: This accomplishes the same thing, I suppose. I think, you know, my bias is always less is more. If you can accomplish the same thing by saying less -- Mark, what do you think? Are we sort of like chasing our tails here? I see the spirit of this question, and Dr. Pfeifer's point is that, you know, why not make it more clear versus getting it out altogether?

MR. MELKERSON: Thank you.

(Laughter.)

DR. KELLY: All right. Let's come up to a consensus. I know Joe's blood sugar is dropping as we speak. Are we in the whole okay with the deletion of this wording?

Yes, Dr. Haines?

Except for Dr. Pfeifer. I'm sorry, Dr. Pfeifer, but majority rules

SO --

Patient Representatives, Consumer Representatives, any other comments?

Well, let's hear from the silent majority. Dr. Lyman, what do you think? You're shaking your head.

DR. LYMAN: Well, this is actually what I was trying to bring up, and I think Dr. Pfeifer did a better job explaining it. But the idea of these are things that we have evidence for, and these are the things they should be used for, so why would we take that out of the indications, out of this warning? Why would we remove the warning?

DR. KELLY: So you --

DR. LYMAN: Because there's been conversations about radiculopathy and other things. I don't understand.

DR. KELLY: So you'd simply add to this --

DR. LYMAN: Because I'm just worried about the --

DR. KELLY: -- small spondy and DDD?

DR. LYMAN: -- expanded indication if we don't -- sorry. I worry about the expanded indication if we don't say this is what we have evidence for.

DR. KELLY: I see.

Dr. Haines?

DR. HAINES: Steve Haines.

This is not the list of indications. This is a warning about things you shouldn't do. We've taken out -- we've reclassified the things you shouldn't do so you don't need the warning anymore. The list of indications needs to include those indications. But this is a warning, not the list of indications.

DR. KELLY: Ronald Jean?

DR. PFEIFER: It says only for. It doesn't say don't use it for. It says only for, but --

DR. JEAN: Just to clarify, 21 C.F.R. 888.3070(b)(1) is actually the Class II indications that have this warning because the Class III indications, which you have just proposed down-classifying to Class II, didn't have data at the time of the original classification. So we're essentially asking you can we remove this warning now, given your recommendation, if that helps.

DR. KELLY: So it's a binary question, either remove it or keep it, not add to it.

DR. JEAN: You can comment on whether you believe the warning needs to be modified, but essentially that warning is saying, you know, you only have safety and effectiveness for the Class II indications, but now you've expanded that with your proposal to down-classify the Class III indications. Confusing?

DR. KELLY: Really, I think in the spirit of concisiveness, maybe adding to this warning, Dr. Jean, would solve the problem of opening it to

other obscure indications instead of -- interested. Is there any downside, Dr. Jean, to adding to the warnings?

DR. JEAN: The warning as written basically is only explicitly stating the Class II indications. You could expand it for the -- you know, to include the Class III indications now. But, again, the question is is the warning necessary at all in the Class II indications section in the first place now that we've made a recommendation on the Class III indications? You could recommend that, but, again, I know this is confusing. The Class III section of 21 C.F.R. 888.3070, we have to actually go out with a proposed order on that portion. And that's what's been the majority of the discussion today.

If we want to modify this down the road in the Class II indications section, that actually requires rule making. And somewhere down the line, we'll probably combine these again so everything's very clean and very easy to read. But, again, we're asking for your feedback, you know, but hopefully that shed some context so you can comment on what you think is necessary.

DR. KELLY: I see Dr. Graf had his hand up first.

DR. GRAF: I agree, because if we're not removing this, we're basically contradicting what we've already said that we're going to downgrade this to a Class II. We've already said that -- come to a consensus that we're going to downgrade to a Class II. I don't know why the warning has to be there as this is no longer applicable to what we've already decided

is our recommendation. I think that just really confuses the issue.

DR. KELLY: I think we have to take a stance -- we can't do both. We can't downgrade, and we can't have these, so I would agree with Dr. Graf on that.

Dr. Pfeifer?

DR. PFEIFER: I was going to change my vote having heard the administrative simplification of the whole thing. In other words, I'm willing to support taking it out.

MR. O'BRIEN: I could support taking it out, but I still have the basic question. What we approved for is downgrading to Class II to use the pedicle screw spine systems as an adjunct to fusion.

DR. KELLY: Right.

MR. O'BRIEN: So to me the warning should still be -- that's still there is the warning should be there's no evidence for safety and effectiveness in non-fusion indications. That's really the warning because that's not going to be part of the indications. The indications are as an adjunct to fusion. So there should be a warning to say there is no indication here as to non-fusion.

DR. KELLY: But how can we reconcile that and still downgrade it to Class II? I don't know if it's possible, Joe.

Dr. Lyman, you have a comment?

DR. LYMAN: I'm going to follow Dr. Pfeifer and change my

position based on the clarification.

DR. KELLY: Dr. Graf?

DR. GRAF: I think to -- Carl Graf. I think to clarify Mr. O'Brien's concerns is that we kind of separated out those non-fusion devices, so by definition this is for a fusion.

DR. KELLY: So are we in consensus that we are all, as we say in Philadelphia, cool with the omission of this warning?

Mr. Melkerson, it's the consensus of this Panel that we are in agreement that the warning as stated may be deleted. Is this a reasonable response, Mr. Melkerson?

MR. MELKERSON: And just to clarify, this is for a future action because we're only looking at (b)(2), so the -- as we're describing, this is something that already exists in the Class II. The things that are currently Class III that you've recommended reclassification of comes across. And I think we'll take Mr. O'Brien's statement, we'll look at what warnings need to be in both, if these are for fusion and not for non-fusion indications.

DR. KAVLOCK: Last one. 21 C.F.R. 888.3070(b)(1) currently requires the following precaution. "Precaution: The implantation of pedicle screw spinal systems should be performed only by experienced spine surgeons with specific training in the use of this pedicle screw spinal system because this is a technically demanding procedure presenting a risk of serious injury to the patient."

Please comment on whether inclusion, revision, or removal of the precaution is appropriate.

DR. KELLY: I think this is the easiest question of the day. Does anyone have any issues with this one? No.

Okay. Thank you.

Mr. Melkerson, with respect to the Question 6c, it is the consensus of the Panel that the inclusion of this precaution is indeed appropriate. Is that an adequate response?

MR. MELKERSON: Yes.

DR. KELLY: I'd like to thank everyone's patience and steadfastness. I would like to thank the FDA for their preparation.

Do you have any summations at this point, FDA, before we conclude?

MR. MELKERSON: The only summation is thank you for wrestling with the difficult questions we posed to you. These are the questions we constantly deal with, so even though I give you a hard time as a panel, you've given similar in return. Your efforts and your discussions and your experience are much appreciated.

DR. KELLY: Well, Mark, I think you do a fantastic job of keeping us all on line here.

I'd like to thank Sara for her babysitting me the last two days. I'd like to thank the Panel and the FDA for their contributions.

And I hereby adjourn the May 22nd, 2013, meeting of the
Orthopaedic and Rehab Devices Panel Meeting.

(Whereupon, at 1:03 p.m., the meeting was adjourned.)

CERTIFICATE

This is to certify that the attached proceedings in the matter of:

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
ORTHOPAEDIC AND REHABILITATION DEVICES PANEL

May 22, 2013

Gaithersburg, Maryland

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.

Cathy Belka

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