SUMMARY MINUTES

MEETING OF THE ORTHOPAEDIC AND REHABILITATION DEVICES

ADVISORY PANEL

OPEN SESSION

September 9, 2005

Hilton Washington D.C. North
Gaithersburg, Maryland

Orthopaedic and Rehabilitation Devices Advisory Panel Meeting

September 9, 2005

Attendees

Acting Chairperson
Sanjiv H. Naidu, M.D., Ph.D.
Pennsylvania State College of Medicine
Hershey, Pennsylvania

Voting Member
Choll W. Kim, M.D., Ph.D.
University of California, San Diego
San Diego, California

Sally A. Rudicel, M.D.
Tufts University, New England Medical Center
Boston, Massachusetts

Consultants
Fernando G. Diaz, M.D., Ph.D.
Detroit Medical Center
Detroit, Michigan

Michael J. Yaszemski, M.D., Ph.D.
Mayo Clinic Graduate School of Medicine
Rochester, Minnesota

Consumer Representative
Connie Whittington, M.S.N., R.N.
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Atlanta, Georgia

Industry Representative
Pamela W. Adams, M.S., R.A.F., C.Q.M.
Etex Corporation, Inc.
Cambridge, Massachusetts

Executive Secretary
Janet L. Scudiero, M.S.

Director, Division of General, Restorative and Neurological Devices
Mark N. Melkerson, M.S.

CALL TO ORDER

Executive Secretary Janet L. Scudiero, M.S., called the meeting to order at 8:04 a.m. She announced the cancellation of the panel meeting scheduled for November 3rd and 4th. Noting that Dr. John Kirkpatrick was unable to attend, Ms. Scudiero read a statement appointing panel member Sanjiv H. Naidu, M.D., Ph.D. as Acting Panel Chair for the September 8th and 9th meeting.

CONFLICT OF INTEREST AND PANEL INTRODUCTIONS

Ms. Scudiero read the conflict of interest statement. A waiver had been granted to Dr. Sally Rudicel. **Acting Panel Chair Sanjiv H. Naidu, M.D., Ph.D.,** stated that the purpose of the meeting was to respond to the FDA's questions on the design of clinical studies for spinal devices to treat mild to moderate low back pain. He asked the panel members to introduce themselves

OPEN PUBLIC HEARING

Sally Maher, Esq., President, Orthopaedic Surgical Manufacturers' Association (OSMA), reviewed the "least burdensome" provisions of the FDA Modernization Act of 1997, the regulatory threshold for PMA approval, and the definition of valid scientific evidence. Congress passed the FDA Modernization Act in 1997 to ensure timely availability of safe and effective new products. The law states that the FDA shall consider the "least burdensome appropriate means of evaluating device effectiveness." FDA has defined least burdensome as successful means of addressing premarket issues that involves the most appropriate investment of time, effort, and

resources. An FDA guidance document states that alternatives to randomized controlled clinical trials should be considered when the potential bias of alternative controls can be addressed and modern statistical methods can be used. The use of scientifically valid surrogate endpoints and Bayesian analyses can be used to predict long-term data based on short-term follow-up.

The regulatory threshold for PMA approval is reasonable assurance of safety and effectiveness as demonstrated by valid scientific evidence. FDA's definition of valid scientific evidence includes alternatives to randomized controlled clinical trials.

Ms. Maher then discussed the specific questions before the panel. With regard to question one, OSMA believes that the decision regarding time to surgically intervene should be dictated by the standard of care for the specific indication. As to question two, OSMA believes that the panel cannot categorically assign a control treatment group to each device category because a demonstration of effectiveness might use alternatives to randomized controlled trials and because the decision should be based on intended patient population and the health benefits the sponsor is seeking approval for. For question three, OSMA maintains that endpoints cannot be categorically assigned to each device type. As to question four, OSMA supports the option to allow both smaller changes in pain and function scores and flexibility in the traditional delta between comparisons of treatment groups based on study objectives and proposed claims of the device. Ms. Maher observed that the questions could not be adequately addressed in the time allotted.

Hallett H. Matthews, M.D., Medical College of Virginia and Mid Atlantic Spine Specialists, gave his own perspectives on the questions before the panel. The guidance provided by FDA should not map designs to device types but should be

flexible. With regard to the first question, Dr. Matthews stated that symptomatic lumbar degenerative disc disease could be viewed as a continuum. Patients early in the continuum could be considered for surgery if symptoms do not subside over several weeks of treatment or if an identified pathology progresses. They could be candidates for nucleus replacement if symptoms do not relent after several weeks or could receive a pedicle screw system if symptoms were long-standing or if the annulus needed retensioning.

As to the second question, Dr. Matthews believed that appropriate controls should to be based on indications and treatment goals, not necessarily on the devices themselves. Also, studies with patients as their own controls, historical controls, or conservative care controls could be appropriate alternatives to randomized controlled clinical trial. Regardless of the control, one should ensure that it represents an appropriate comparison treatment.

With regard to the third question, Dr. Matthews emphasized that the devices in question were not spinal fusion devices, so the 12 to 24 month data historically required might be unnecessary since there would be no need to allow time for the spine to fuse. Twelve months or less might be sufficient time to determine safety and effectiveness for early intervention non-fusion devices. Furthermore, device effectiveness should be based more on alleviation of pain and restoration of function rather than on radiographic measures. Emphasis should be placed on early postoperative data since these devices were intended to provide benefit early on. Dr. Matthews suggested that radiographic criteria should not be a primary endpoint.

As to the final FDA question, he suggested that the success criteria and statistical approach should take into consideration that the types of devices being discussed were generally intended for earlier stages of disease and, in some cases, required less surgical trauma and rehabilitation.

Dr. Matthews concluded by saying that these devices could be evaluated using approaches less burdensome than current IDE study designs and smaller studies based on shorter-term endpoints should be used with longer-term post-market patient observation. He also encouraged innovation and flexibility in study designs.

Ronald K. Smith, Director of Quality Systems and Regulatory Affairs, Spine Wave, Inc., commented on the time course of treatment for possible candidates for nucleus replacement or augmentation. Mr. Smith first described Spine Wave's NuCore Injectable Nucleus, an in situ curing material that adheres to the existing nucleus pulposus and annulus and mimics the disc nucleus in protein and water content, pH, and mechanical properties. It replaces only as much nucleus as has been removed, and its shape is determined by the space into which it is injected. The physical, chemical, and mechanical properties of the device allow for multiple potential intended uses.

The device would be considered a nucleus replacement device for treatment of acute and chronic degenerative disc disease, but the treatment modalities for each would be different, and a clinical study would likely require a different control group for each use.

Mr. Smith noted that the length and type of conservative care a patient should receive prior to use of such a device would depend on the clinical condition, not the classification of the device. The physician should follow guidelines such as those of the

American Academy of Orthopaedic Surgeons (AAOS) or the Agency for Healthcare Research and Quality in making treatment decisions. These guidelines establish courses of treatment for different diagnoses; they state that a full course of nonoperative treatment should be first considered unless a patient clearly falls within the clinically severe category. FDA has typically required a six month conservative treatment period for studies intending to treat any degree of lumbar degenerative disc disease, much longer than the four to six weeks recommended by AAOS for herniated nucleus pulposus. Mr. Smith recommended that the FDA adopt a guideline such as that of the AAOS.

Reginald J. Davis, M.D., Greater Baltimore Medical Center, discussed the progression of lumbar degenerative disease, which represents a broad spectrum of a complex cascade of processes. Early in the disease, though there may be pain, there is maintenance of disc height and relative maintenance of hydration. With moderate disease there is loss of disc height and hydration, as well as some annular fissures, end plate changes, or early Modic changes. Severe disease is characterized by disc space collapse, vacuum phenomenon, and similar stratification of other structures. By looking at the stratifications of the disease, patients, and treatment options, guidelines for the devices can be developed.

Paul C. McAfee, M.D., Towson Orthopedics Association, Baltimore, discussed the Abbott Spine Wallis interspinous process spacer. The first IDE approved clinical trial used total disc replacement and a posterior lumbar interbody fusion (PLIF) with pedicle screws as the control group, but the investigators believed that the control group was a larger magnitude of procedure than the Wallis. It is a non-rigid fixation system, does not use pedicle screws, is intended for degenerative changes less than

Pfirrman State V, and has been shown to reduce the extremes of flexion and extension by 35 percent.

The advantages of the Wallis device are that it's a largely soft tissue procedure that can be performed outpatient with no general anesthesia. Only the interspinous ligaments are removed, rather than any of the spinal column. The rehabilitation is fast, and the device can be removed without fusion or anterior vessel dissection. The procedure is very safe; 16 year survivorship is 82.7 percent with 58 percent follow-up.

VAS decreased from a mean of 70 down to 15. Fifty-five matched sets of MRI, pre-operative and at one year, showed rehydration of the nucleus pulposus in a majority of cases.

The preferred experimental design was the Wallis device compared to conservative treatment plus a rescue procedure rather than conservative physical therapy. The rescue is fusion or arthroplasty. At six months both the Oswestry score and the VAS were very predictive of 24-month results. Another advantage is that the Wallis leaves open the option for fusion or total disc replacement.

Dr. McAfee talked about the Pfirrman classification system. At Stage I physical therapy and epidural injections are appropriate. For a collapsed disc, PLIF and disc replacement are appropriate. The Wallis is intended for patients with intermediate degeneration, Pfirrman II, III, and IV. He talked about Pollintine's work and noted that irreversible changes in the facet joints only occur once a patient reaches Stage IV, so there are three stages of degenerative changes involving only the anterior column. Interspinous devices aim at earlier intervention to preserve the posterior facet joints.

Dr. McAfee said that he would try for delta of 15 percent versus 10 percent because the procedure can be done on an outpatient basis with local anaesthesia, rehabilitation is faster, and the procedure is reversible. He also stated that he was willing to accept five percent lower success rate compared to the more invasive total disc replacement or PLIF because the procedure is reversible and largely superficial, just under the lumbar facet between L1 and L4.

Brent A. Blumenstein, Ph.D., TriArc Consulting, Seattle, proposed a study design for the class of devices being discussed. There are three types of intervention for DDD: conservative, early invasive, and late invasive, each with its own invasiveness, risk, and possibility of subsequent intervention, and these features influence the kind of outcome sought. While traditional late invasive interventions focused on failure to realize or sustain success, Dr. Blumenstein proposed an outcome of durable response, or the realization of the state of response for all assessments spanning at least X months, with X proposed as six months.

The statistical endpoint proposed was time to durable response, the interval between randomization and when the durable response is observed to start, but this is subject to competing risk, an event that prevents observation of the endpoint.

For trials of early invasive intervention, there is no approved predicate to use for the control arm, so the only choices for control are conservative care and late intervention. A late invasive intervention control could be superior to the early invasive intervention being studied since the early intervention has less risk and does not preclude subsequent intervention, but an acceptable degree of inferiority must be defined. This could be called an acceptable inferiority trial.

A superiority trial would use conservative care as the control, and an appropriate endpoint would be time to durable response. But problems would arise if the early intervention was almost certainly superior with regard to evaluation of long-term effects. An alternative is conservative care with rescue, which would allow the control arm to catch up to the early invasive intervention when it was almost surely superior to just conservative care. The rescue would be implemented only in the control arm and should not be early invasive intervention but rather something more, a late invasive intervention.

Two endpoints were proposed for this type of trial. The primary or short-term endpoint would be time to durable response from the first intervention. The co-primary or long-term endpoint would be durable response cumulative incidence at time Y, with Y defined as one year. The conservative care durable response would include the rescue and ignore failure of conservative care.

Dr. Blumenstein stated that it would be onerous to require the investigational arm to be superior in the long run to the late intervention. Therefore, one could test for either non-inferiority or acceptable inferiority.

Eeric Truumees, M.D., Weissman, Gitlin, and Herkowitz and William Beaumont Hospital, Royal Oak, Michigan, acknowledged the FDA's concerns about early intervention devices and noted that nonoperative options must be considered. Understanding an implant's effects requires appropriate comparisons and sensitive outcomes measures. Dr. Truumees believed that the questions posed made false assumptions about similarities among these devices, which have different goals, intended patient populations, mechanisms, and surgical morbidities. Controls, nonoperative

treatment periods, and outcomes measures should be based on patient population, disease state being studied, and device claims rather than on the particular category of devices.

With regard to the first question, due to the heterogeneity of patients, physicians, investigators, and study sponsors should set standards of care rather than a regulatory body such as the FDA. Those with similar symptoms will not necessarily have similar radiographs and vice versa. Furthermore, delayed intervention may necessitate a more invasive approach later. Dr. Truumees observed that while some non-surgical treatment would always be appropriate, percutaneous placement of some implants blurs the lines between traditional nonoperative and operative care, and one cannot dictate what period of or types of nonoperative care are appropriate for new devices.

As to the second question, a control group should be chosen by the investigators and sponsor based on patient population and the health benefit sought. As an example, differences in method of implantation, whether percutaneously or open surgery, will lead to different ideal control groups. While nonoperative care may not always be an appropriate control, patients must be allowed to cross over when appropriate in cases where a nonoperative control is used.

With regard to the third question, Dr. Truumees stated that endpoints could not be categorically assigned to device types because of marked differences in the goals of each device. Similarly, length of follow-up should be based on intended use and proposed benefits. Because of the less invasive strategies used for some of these devices, outcomes might become clearer much sooner.

As to the fourth question, Dr. Truumees supported allowing sponsors to specify study design based on population studied and objectives of the device rather than the outward appearance of the device.

Philip L. Schneider, M.D., Howard University, spoke on behalf of the North American Spine Society. With regard to question one, he said that time to intervention would depend on patient pathology, but since these devices would be intended for earlier intervention, time to intervention would be shorter. DDD represents a wide array of disorders, and different levels of disease require different approaches. As to question two, he noted that fusion may not be an appropriate control for studying less invasive devices because it may be too aggressive for the pathology being studied, controls for various disease states may need to be different, and the goal of treatment is to provide a stable platform that allows motion, the antithesis of fusion.

Addressing question three, Dr. Schneider noted that since the devices would be intended for motion preservation rather than fusion, the endpoints would likely occur prior to the traditional 24 months used for fusion studies. Endpoints should be flexible based on the device and the level of disease being treated. As to question four, he noted that smaller changes in outcomes would be inevitable for earlier interventions for milder disease states.

Paul Anderson, M.D., University of Wisconsin, noted that the panel was looking at devices for lumbar DDD in patients with mild to moderate back pain, whereas patients may experience back and leg pain with some degenerative conditions. He emphasized the appropriate use of clearly defined terminology in clinical trial design.

Given that definitions for success and failure for patients with mild to moderate symptoms have not been agreed upon, Dr. Anderson observed that there was no solid foundation upon which to judge effectiveness for these devices and noted that defining clinically significant response was necessary to determine success. He observed that success and failure would be dependent on what the patient was willing to undergo. Dr. Anderson also pointed out the lack of established guidelines for timing of intervention.

The most important metric for outcomes is the patient's satisfaction in the context of the treatment provided. In a recent paper, Walsh and colleagues established patient satisfaction as a gold standard. With regard to clinical success for mild to moderate symptoms, the consensus of outcomes experts is that the minimum clinically important difference (MCID) is the appropriate standard. MCID is particularly relevant when applied to these patients when there is significant risk of false negatives due to ceiling effects. Clinically significant levels of improvement need to be defined, not chosen arbitrarily as the FDA did in choosing an absolute 15-point change from baseline in the ODI score for back pain studies. In an article by Mannion et al., a good outcome was defined by a cut-off value of 11 points using ROC analysis, and the MCID for an individual patient was 9 points. The authors also recommended using percent change from baseline and acknowledged that the cut-off for patients treated conservatively may be in the range of 4 to 6 rather than the 11 points used for operatively treated patients.

Furthermore, the ODI has been reported to be less sensitive for patients with mild to moderate disability. Dr. Anderson stated there was no evidence that a 15-point change from baseline in the ODI was a scientifically valid measure of MCID in mild to moderate patients.

Appropriate thresholds of clinical significance to define success in individual patients must be validated. The large difference in risk between current operative treatment and nonoperative therapy must be taken into account. With regard to controls, nonoperative therapy is the standard of care for patients with mild to moderate symptoms. Dr. Anderson also raised the ethical issue involved with randomly assigning a patient with mild to moderate symptoms to invasive and risky surgical procedures. Investigational and control therapies with comparable risks and benefits must be selected. For interspinous spacers, nonoperative care is an appropriate control since neither would expose patients to the risks of neural injuries and general anesthesia and both keep future treatment options open.

Dr. Anderson concluded by stating that clinical studies evaluating devices must take into account the risks and benefits of any therapy, clear and consistent application of terminology, the patient's level of satisfaction, and the strengths and limitations of outcomes instruments.

Steven Hochschuler, M.D., First Vice President, Spine Arthroplasty Society, addressed the change in spinal surgery from stabilization by fusion to stabilization by motion preservation. He advocated a rethinking of the entire clinical study process to expedite development of new technologies while protecting patients, and posed some questions that needed to be addressed.

The first question posed by Dr. Hochschuler was whether the proposed device was considered minimally invasive, minimally destructive, and readily reversible or salvaged. He stated that these devices would be justified earlier in the treatment process

as their efficacy would be compromised by the traditional six months of failed conservative care.

The next question was whether the proposed device has any potential to prevent the degenerative cascade. Success of early intervention may be less likely if the degeneration progresses to the point that there is loss of disc height, chronic muscle spasm, and facet disease. Dr. Hochschuler next asked whether six weeks to three months of incapacitating low back pain as defined by various measures was enough to merit surgical intervention, and he suggested that it depended on the nature of the surgery and the risk profile of the device.

The fourth question he asked was whether more than three months of conservative care was more intrusive to the patient's well-being than a minimally invasive reversible procedure, and he noted that it would be unethical to prohibit patients from surgical care if they were not responding to conservative management.

Next Dr. Hochschuler asked whether early, minimally invasive, motion-preserving surgery might spare the patient from the issues associated with being unemployed. Early intervention may halt the degenerative cascade, and the longer one is incapacitated the less likely that individual will make a full recovery. There would also be the potential to save society from the significant financial burden of worker's compensation claims.

The final question Dr. Hochschuler addressed was what criteria other than safety and efficacy patients were most interested in. He said they were relief of pain, return to function, and prevention of downstream degeneration.

FDA PRESENTATION

Jonathan H. Peck, Orthopedic Devices Branch, Office of Device Evaluation, began by giving background information on mild to moderate lumbar degenerative disease. Chronic low back pain is a leading cause of employee absenteeism and disability. The causes are varied. The clinical significance of a bulging or degenerated disc is unclear. A study by Boden showed that a majority of patients over 60 show radiographic signs of disc disease without having any presenting symptoms.

As to treatment options, most patients are successfully managed nonoperatively. Spinal fusion, decompressive procedures, and more recently, total disc replacement are the surgical options for patients whose symptoms persist or progress. Less invasive procedures for disc herniation and more minimally invasive approaches for laminectomy and spinal fusion have been developed.

Recently devices that fall somewhere between nonoperative and more invasive surgery have been developed to stabilize the spine and maintain some degree of motion. These devices vary widely and consist of three types: spacers, nucleus replacements, and pedicle screw based systems.

Patient inclusion parameters may need to be changed to study patients who fall earlier in the continuum of the disease. The FDA framed questions for the panel to consider with regard to intended study population, potential control groups, appropriate study endpoints, and other issues concerning study design.

Risks associated with permanent implants may not be appropriate for patients with mild to moderate disease. Possible control arm options are nonoperative care, with

or without a crossover or rescue procedure, or surgeries such as fusion, total disc replacement, or laminectomy. There are potential limitations to both approaches.

Randomization to nonoperative care for patients who have previously exhausted nonoperative options may be inappropriate and may lead to a low success rate for the control. On the other hand, if nonoperative options are not exhausted, any outcomes observed may not be a result of the device, and there may be ethical issues associated with treating mild to moderate disease with an implant. There is also potentially significant bias due to placebo effects associated with nonoperative care as opposed to surgical intervention.

Furthermore, traditional spine study endpoints may not be the most appropriate to evaluate mild to moderate disease. Potentially lower baseline scores for pain and function may lead to a ceiling effect.

Mr. Peck then read the FDA questions.

PANEL DELIBERATION AND FDA QUESTIONS

Mr. Melkerson stated that the panel could address the various claims associated with the three device types or the device types themselves.

Dr. Yaszemski opened the panel's deliberations with his remarks. He stated that his conclusion was that it was not yet appropriate to provide strict answers to any of FDA's questions because evaluation of these devices was still in the early stages. Instead, he believed it was appropriate to provide a framework with which to evaluate each particular device.

Dr. Yaszemski emphasized equipoise. When a patient is randomized, the risks and benefits of each treatment must be equal according to the best knowledge available. To achieve equipoise, he stated that there were two issues, clinically appropriate care and scientific validity.

Dr. Yaszemski next discussed two examples to illustrate the heterogeneity of the patient groups and his point that the panel could not provide firm or rigid guidelines at this time. First a young patient previously asymptomatic who had an event and has back and leg pain, and second a person with degenerative spondylolisthesis and spinal stenosis who is less and less able to complete his or her daily activities. Devices also vary in terms of risk and benefit. Reversibility is an important consideration in terms of how the device is removed and what anatomy will stay altered.

Dr. Yaszemski returned to his examples and asked whether six weeks of nonoperative treatment was long enough to consider use of a device. He proposed that for the first patient it would not be appropriate to move to a minimally invasive procedure but that for the second example it might.

He then looked at the risks associated with each device type. For pedicle screw-based systems, the paraspinal muscles may have to be retracted, and there is risk of injury, though minimal in experienced hands, to vascular and neurologic structures. These devices can be removed. For interspinous process spacers, local anesthetic can be used, the risk to vascular and neurologic structures is very small, and they can be removed with minimal alteration of the normal anatomy.

As to prosthetic fixed disc nuclei (PDN), if it is injectable and the patient was already having a discectomy as part of the study, the risks of surgery and anesthesia have

already been accepted. If the patient is not otherwise having an operation, the same device must undergo different scrutiny. If the PDN is not injectable, there will similarly be a different level of scrutiny.

Dr. Yaszemski concluded by stating that over time patterns that emerge will allow for more complete answers to the FDA's questions.

FDA QUESTIONS

1. Considering the natural history of most cases of lumbar degenerative disease, please discuss the appropriate time to intervene with a permanently implanted device intended to treat mild to moderate disease. Then please discuss the characteristics that should be used to define patients who are appropriate candidates for earlier surgical intervention. At a minimum, please consider:

- **The amount and type of nonoperative care a patient should receive prior to inclusion in a spinal device clinical trial.**
- **The specific baseline criteria (e.g., ODI, VAS, neurologic findings, radiographic criteria) that patients should meet prior to inclusion.**

There was consensus among panel members that, given the heterogeneity of patients, disease, and the devices themselves, they were unable to give a broad answer regarding appropriate time to intervene, but panel members agreed that earlier surgical intervention would be appropriate in some cases. One panel member pointed out that there should be consideration of the conservative care given by a patient's primary care physician prior to a given study. Another panel member noted that there was still much to be learned from clinicians about these devices with regard to standard of care, time to intervention, and appropriate endpoints.

Panel members also agreed that inclusion and exclusion criteria should be based on what combination of disease, patient group, and device was being studied and that specificity would enable an appropriate answer to the question.

2. Based on the population of appropriate surgical candidates discussed in Question #1, please discuss the control group options, operative or nonoperative, for these devices intended to treat mild to moderate lumbar degenerative disease. Please consider:

- **A clinical study must be designed to demonstrate a treatment effect. For example, it must be designed to show that any observed clinical outcome is due to the device rather than other confounding factors and treatments.**
- **Typically, in order to warrant surgical intervention for lumbar degenerative disease, a patient should have exhausted nonoperative therapy options; however, a patient should not be randomized to a control treatment that they may have already "failed."**
- **The intended patient population does not necessarily meet the criteria established for more invasive surgical options such as fusion, total disc replacement, or laminectomy.**
- **The potential for crossover or secondary treatment options. Specifically, please comment on how to define patients who have "failed" the first treatment and thus are eligible to go on to receive the second treatment.**

Most panel members agreed that a randomized nonoperative control group would be necessary and that historical and crossover data should not be used. Some panel members were concerned about the practicality of that approach. Patients who fail treatment should be treated outside of the study and not used for crossover data. Some panel members thought that enrolling and randomizing patients earlier in the course of treatment would be beneficial and help with the crossover issue in that patients would be less likely to have failed the nonoperative treatment control option.

In response to a clarifying question, the panel was in general agreement that there was no surgical treatment in use in the U.S. for mild to moderate low back pain that could serve as an appropriate control. An FDA representative asked whether it was ethical to randomize a patient to surgery who might improve through conservative care, and the panel members agreed that the decision should be left up to the patient, so long as the investigator believed there was equipoise in the treatments being compared and had explained the risks and benefits of each.

The FDA then asked specifically about controls for acute conditions and more slowly developing conditions where six-month inclusion criteria might be used. One panel member stated with regard to the slowly developing conditions that nonoperative treatments such as activity modification, anti-inflammatories, and physical therapy would likely be an appropriate control for a surgical option. Another panel member added that a metric might be used to determine how much the disease had progressed and was affecting the patient's life. Some panel members believed that a patient's previously undergone conservative care would not be an appropriate control given the variation in conservative care among clinicians.

Some panel members believed that a study from outside the U.S. that had valid outcome measures, was well controlled, randomized or not, and had a good historical control could provide enough data to reasonably determine that the device was safe and effective. One panel member countered that there could be reimbursement issues if the studies used did not come to the level required by the reimbursing agencies. Another panel member suggested that the criteria for a good study should be evidence-based medicine, regardless of where the study was conducted. One panel member noted that the bar for reimbursement was very different from what Congress had asked the FDA to do with respect to safety and efficacy studies.

3. Please discuss the most appropriate clinically significant endpoints to evaluate subjects with mild to moderate lumbar degenerative disease at baseline. Specifically please discuss:

- **The value, if any, in demonstrating a faster response as opposed to comparing responses at the final study evaluation time point, which has traditionally been 24 months for spinal studies. If demonstrating a faster response is considered important, please discuss the length of time the response should last to consider the device a success.**
- **The value of potential mechanism of action endpoints. For example, please discuss whether or not sponsors should include endpoints to demonstrate**

(through objective radiographic criteria) restoration in disc height and disc hydration.

- **Potential endpoints that could demonstrate earlier intervention is warranted because it alters or delays the course of the disease.**

Panel members agreed that in general the traditional 24 months would not be needed, the time point should be based on the condition being treated and the device. With regard to mechanism of action endpoints, panel members believed they had some value but that patient-oriented outcomes were more important. Some panel members noted that using the same validated tools across the board would be helpful.

The FDA asked a clarifying question regarding the duration of effect before moving on to a more invasive surgical procedure if earlier endpoints were used. The panel was in general agreement that it would depend on the risk of the specific implant, the amount of alteration of the normal anatomy, and the ease with which the device could be removed. One panel member responded that it would depend on whether one was looking at early success response or delayed sustained response.

FDA then asked about different types of evaluations and whether the agency should get input from the professional societies. Panel members concurred that the answer would depend on the disease and the device.

FDA then asked, with regard to a situation in which no claims about mechanism of action were made, how one could be sure that patients who improved would not have done so had they continued with conservative care. A panel member responded that the issue would be addressed by an appropriately designed study with an appropriate control group.

4. Please discuss what changes to traditional spinal device study designs might be appropriate given the less invasive nature of many of these devices as well as the mild to moderately affected patient population. Please discuss:

- **The appropriate final time point to evaluate the study endpoints and make a determination of overall study success.**
- **Whether it is appropriate to define a smaller change in pain and function scores as clinically significant given that these devices may pose less risk and the inclusion score may be lower leading to concerns about the potential for a ceiling effect.**
- **Non-inferiority versus superiority study designs, depending on the study control.**
- **Whether using a delta value larger than the traditional 10% may be appropriate depending on the control.**

In general the panel believed that if the device was less invasive, then smaller changes in pain and higher delta values might be acceptable. The parameters should be based on the specifics of the particular study. One panel member favored a larger delta in exchange for earlier intervention for a minimally invasive treatment.

The FDA asked for clarification of what would be considered less invasive and minimally invasive. The panel members were in agreement. An injectable nucleus replacement done concurrently with another surgery does not lead to any increased risk. An injectable percutaneous nucleus replacement is minimally invasive. An open surgically implanted nucleus replacement would be characterized as a standard surgical procedure, neither less nor minimally invasive. Pedicle screw systems implanted percutaneously under local anesthesia are considered less invasive, and those requiring open surgery are neither less nor minimally invasive. Interspinous process spacers are minimally invasive.

ADJOURNMENT

Dr. Naidu thanked the panel members and adjourned the meeting at 11:48 a.m.

I certify that I attended this meeting of the Orthopedic and Rehabilitation Devices Advisory Panel Meeting on September 9, 2005 , and that these minutes accurately reflect what transpired.

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Janet L. Scudiero
Executive Secretary

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

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Sanjiv H. Naidu, M.D., Ph.D.
Acting Chairperson

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10-18-05 Edited JLScudiero, small changes
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11-08-05 pre TRStevens 2 minor edits, JLS