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Food and Drug Administration, Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

RE: Proposed Classification of Pedicle Screw Spinal Systems
[Docket No. 95N-0176]

On behalf of Public Citizen's Health Research Group, we submit the following comments regarding the FDA's proposals to classify certain unclassified preamendments pedicle screw spinal systems--used in conjunction with spinal fusion surgery--into class II (special controls) and to reclassify certain postamendments pedicle screw spinal systems from class III (premarket approval) to class II. As we will explain in this document, we strongly oppose the FDA taking these actions because pedicle screws have never been proven to be either safe or effective and the application of the weaker regulation--special controls--will not be sufficient to protect public health.

KEY POINTS ADDRESSED IN THIS DOCUMENT

1) Pedicle screws have never been proven to enhance spinal fusion or improve clinical outcomes of fusion surgery.

2) The Historical Cohort Study provides an insufficient basis on which to determine the safety and efficacy of pedicle screw spinal systems because of significant flaws in study methodology and interpretation.

3) The only three prospective, randomized, clinical studies of pedicle screw spinal systems conducted to date demonstrated no benefits from using pedicle screws to enhance spinal fusion surgery in patients with spondylolisthesis or spinal stenosis.

4) No reliable studies have been conducted that compare pedicle screws to other treatments for the treatment of spinal fracture, scoliosis, spinal tumor, or any other chronic or acute instability.

5) Pedicle screws subject patients to unique intraoperative and post-operative events that can significantly increase complications including neural damage, infection, and the need for additional surgical procedures.

6) Pedicle screw manufacturers have shown blatant disregard of U.S. law and FDA regulations by openly--and illegally--promoting off-label use of these devices.

7) There is insufficient information to determine what types of special controls could provide reasonable assurance of the safety and effectiveness of pedicle screw systems or to establish performance standards to provide such assurance.

8) We call upon the FDA to take the following actions in regulating pedicle screw spinal systems:

- Retain the class III classification of pedicle screws until randomized, prospective, clinical trials elucidate the benefits and risks of these devices.

- Require manufacturers to submit acceptable premarket approval applications demonstrating the safety and effectiveness of pedicle screw spinal systems prior to marketing any further systems.

- Classify the unclassified preamendments pedicle screw spinal system intended for the treatment of severe spondylolisthesis of the fifth lumbar vertebrae into class III.

- Move immediately for substantial criminal or civil penalties against each manufacturer that illegally promoted the pedicle screw systems.

BACKGROUND INFORMATION

One year ago, Public Citizen's Health Research Group petitioned the FDA to remedy the illegal promotion and gross overuse of pedicle screw spinal systems. We urged you to: (a) declare a moratorium on most uses of pedicle screws until manufacturers demonstrated their safety and effectiveness, (b) reject the FDA Advisory Panel's recommendation to down-classify pedicle screws from class III to class II for degenerative spondylolisthesis and spinal fracture, (c) pursue criminal or civil penalties against manufacturers who illegally promoted the systems, (d) require large box warnings labeling the devices, and (e) require each patient receiving an implant to sign an FDA-approved consent sheet.

The FDA took none of our recommended actions. Instead, it granted clearance to at least 10 manufacturers to market pedicle screw systems through the 510(k) process--a procedure that requires manufacturers only to demonstrate that their devices are substantially equivalent to spinal systems on the market prior to the enactment of the Medical Device Amendments on May 28, 1976--without providing evidence of safety or effectiveness. Furthermore, the current FDA proposal to classify pedicle screw spinal systems as class II medical devices for most types of acute and chronic instabilities and deformities will guarantee that reliable safety and effectiveness data will never be collected.

Such an action by the FDA would be a grave mistake. Despite the wide-spread off-label use of these devices, these facts remain: (1) pedicle screws have never been proven to enhance spinal fusion or improve clinical outcomes of spinal fusion surgery; (2) pedicle screw systems have been associated with significant and unique complications that cause functional deficits, pain, and the need for additional surgical procedures; (3) pedicle screw manufacturers have shown blatant disregard of U.S. law and FDA regulations by openly promoting off-label use of these devices; and (4) there is insufficient information to determine whether or what types of special controls could provide reasonable assurance of the safety and effectiveness of pedicle screw systems or to establish a performance standard to provide such assurance considering the wide range of system designs, manufacturing processes, patient diagnoses, and physician skills.

Since our original petition was filed, pedicle screw abuse and overuse has continued. An estimated 50,000 pedicle screw systems are implanted in the United States each year (Hanley, 1993). More than 3,000 lawsuits against implant manufacturers have already been consolidated in multidistrict litigation claiming injured patients were not informed of the risks, off-label use, or investigational status of pedicle screw systems (Levin, 1995). In the two most recent quarters for which we have data (April-September, 1995), 64 Medical Device Reports about pedicle screws were submitted to the FDA. As is the case with most medical devices, this number probably represents less than 10% of the problems actually encountered.

We have recently obtained new information that reinforces our concerns about pedicle screw spinal systems. Further review of published literature and affidavit testimony from the pending multidistrict litigation In Re: Orthopedic "Bone Screw" Products Liability Litigation, MDL Docket No. 1014, have provided us with material that substantiates our concerns and raises

additional questions about the actual rate of complications associated with pedicle screws.

We therefore reiterate our previous recommendations and urge the FDA to retain the Class III status of pedicle screw systems--thereby restricting their sale and use until they have been proven to be safe and effective for the indications for which they are widely used.

PEDICLE SCREWS HAVE NEVER BEEN PROVEN TO ENHANCE SPINAL FUSION OR IMPROVE CLINICAL OUTCOMES OF FUSION SURGERY

The Historical Cohort Study

The Historical Cohort Study formed the basis both for the Orthopedic and Rehabilitation Devices Panel's recommendation to down-classify pedicle screws for the treatment of degenerative spondylolisthesis and spinal fracture and for the FDA's proposal to expand the use of the devices for the treatment of acute and chronic instabilities and deformities (Federal Register, 10/4/95). But this study should support no such conclusions because it contains systemic errors in methodology and interpretation. These errors are so significant that the cohort study seems to have been designed in order to support the down-classification of pedicle screws from class III to class II--rather than to evaluate the outcomes of pedicle screw systems. With its biased approach, faulty methods and interpretations, and lack of peer review, the study appears to be more a large-scale advertisement for pedicle screws than a valid piece of scientific evidence.

Issues in Study Design

From the outset, the historical cohort study was described as an opportunity to vindicate pedicle screw spinal systems. According to the authors, the purpose of the cohort study was to provide the FDA with valid scientific evidence "to determine that pedicle screws could be considered as class II devices, rather than class III devices" (Yuan, Garfin, Dickman, & Mardjetko, 1994). This lack of objectivity is unacceptable; no scientific study should be designed to prove a predetermined outcome.

Issues in Study Methods

The methods used in this study were inadequate to collect the information needed to draw conclusions about the safety and effectiveness of pedicle screw systems. Several of the problems with the study's methodology are discussed below.

First, the patient-inclusion criteria were poorly defined. Only patients with diagnoses of degenerative spondylolisthesis or spinal fracture were included in this study. But degenerative spondylolisthesis is a poorly-defined term that can mean any type of displacement of the lumbar vertebrae caused by the degeneration of the intervertebral disk and facet joints. This condition can range from quite severe, with actual displacement of 6 millimeters or more, to quite mild, with apparent displacement merely an artifact of x-rays (Nachemson, 1995). Since this study did not specify degree of spondylolisthesis, it is likely that a wide range of displacements were used--including some that required no stabilization at all--precluding the possibility of a uniform

cohort.

Second, the case report form was poorly designed. This form asked physicians to record subjective outcome parameters about their own patients. The case report form did not encourage reporting of multiple re-operations or complications of the same type. For example, no matter how many times a patient required surgical modifications, the physician was only required to report "yes" under re-operations.

Third, the study erred in using fusion as an outcome measure. The biologic rationale justifying lumbar fusion is the concept that lumbar instability causes pain. However, in most cases, instability is neither clearly defined nor measurable (Franklin, Haug, Heyer, McKeefrey & Picciano, 1994). In fact, there is no evidence that fusion or lack of fusion has any bearing on clinical outcomes. Several studies have demonstrated that up to half of all patients who have clear radiographic evidence of pseudoarthrosis, or lack of spinal fusion, have no symptoms (BackLetter, 1994).

Nevertheless, most published reports about pedicle screws use fusion status as the primary outcome measure. These outcomes should be considered highly suspect because conventional imaging methods can not reliably ascertain fusion status in the presence of metallic pedicle screw implants. Many studies have confirmed that true fusion rates can be determined only through surgical re-exploration. In 1991, Brodsky, Kovalsky & Khalil compared radiologic assessments of lumbar spine fusion with surgical exploration in 175 patients. They found no correlations with actual spinal fusion in 36% of plain roentgenographs, 41% of polytomograms, 38% of bending films, and 41% of computed tomographic scans. The authors concluded that radiologic inaccuracy was manifest on both the positive and negative sides with a significant percentage of inaccuracy in all radiologic methods used. A study by Larsen (1994) confirmed these results. He examined 33 patients undergoing diagnostic testing for back pain following instrumented spinal fusion and compared the results of four different imaging methods with actual fusion status observed during surgical exploration. Correlations with true fusion rates were present in only 39% of lateral and anteroposterior x-rays, 60% of flexion-extension radiographs, 38% of CT scans, and 40% of bone scintigraphs. A further report by Pinto (1994) demonstrated that single-photon computed tomography (SPECT) was only able to capture evidence of non-union in 50% of pseudoarthroses.

According to Dr. Alf Nachemson, a world leader in the field of back pain, a senior editor of Spine Journal, and the 1995 recipient of the Bristol-Myers Squib Zimmer Award for Excellence in Orthopedic Surgery, the only reliable method of determining the occurrence of bony fusion other than visual examination of the fusion mass is by stereophotogrammetry. This method, developed by Selvik in 1989, has been used only rarely, but it offers great promise for future research. The method involves the insertion of three small tantalum ball bearings into each of the vertebrae included in the fusion. Later, these ball bearings are visible in x-rays, allowing exact evaluation of spinal mobility. According to Dr. Nachemson, stereophotogrammetry should be a routine addition to all fusion operations since it is the only accurate, non-invasive method of determining the extent of spinal fusion (Nachemson, 1995a).

At this time, neither surgical re-exploration nor stereophotogrammetry are routinely used in clinical studies. Thus, the reports of fusion status can not be considered reliable and should not be used as outcome measures. Instead, as discussed by Zdeblick (1993), "a greater emphasis should be placed on clinical results, rather than radiographic results."

A fourth serious problem with the methodology was that the follow-up period was too short to identify all potential complications. Although the study period was chosen to allow a two year follow-up for all patients, the final evaluation time was not defined and was left to the surgeon's discretion. As a result, there is no way of knowing whether all or even most of the potential complications were identified. In fact, the authors of the cohort study themselves observed that the rate of functional benefits was lower among patients followed for more than 24 months than among patients whose final assessment was nearer the time of surgery (Yuan et. al., 1994). In addition, since the study protocol required physicians to report complications only within a two year period, many late complications may have been disregarded.

Finally, the methodology was flawed due to the loss of patients to follow-up. Only patients with complete records (i.e. pre- and post-surgery) could be included in this study. An incalculable number of patients were excluded from analysis because they did not return to their surgeon for follow-up or because their surgeon kept incomplete records. There is no discussion about the patients who received procedures but were not included in the study. This information is important because the results of a cohort study are only reliable if patients studied are representative of the population of all patients receiving the intervention. It is likely that patients with poor results never returned to the surgeons who caused them such pain. Since no discussion of excluded patients was provided, it is impossible to determine if there were significant differences between those included and those excluded from the study. As a result, we cannot determine if the population included in this report was a representative sample of the greater population of people who received pedicle screw implants.

Issues in Study Interpretation

Bias and confounding can significantly alter study outcomes if they are not accounted for in study design or analysis. The historical cohort study of pedicle screw systems did not sufficiently address these issues, and thus the already-minimal benefits reported from pedicle screw use must be further questioned. Furthermore, the study design was not sufficient to support the types of cause and effect relationships claimed by the authors.

In our previous communication with the FDA regarding this device, we discussed the problem of selection bias. Selection bias occurs when the identification of individual subjects is based on the outcome of interest. It can occur with differential surveillance, diagnosis, or referral of individuals into the study (Hennekens & Buring, 1987). In his review of the Historical Cohort Study, Yahiro (1994) noted that "...surgeons with predominantly good or bad results may contribute data differentially or may contribute only selected cases from their practices."

The research protocol asked surgeons voluntarily to submit case reports on patients meeting certain inclusion criteria. Since surgeons were told that the purpose of the study was to prove

that pedicle screws are safe, it is likely that physicians with poorer results were less eager to submit case report forms than physicians with better results. In addition, although physicians were instructed to provide data on all patients meeting certain criteria, there was no surveillance to ensure that they selected consecutive or comprehensive cases. In fact, each physician enrolled an average of only 11 cases in the study. Since most orthopaedic surgeons probably performed more than 11 pedicle screw implantations in patients with spondylolisthesis or spinal fracture over the two-year period, it is likely that a significant amount of selection bias occurred.

An even more significant source of error is recall bias. This study evaluated treatments that occurred at least two years prior to data collection, so it depended on the availability of relevant data in adequate detail from pre-existing records. Since these data were recorded for purposes other than scientific investigation of the hypothesis of interest, not all necessary data could have been available. To resolve this problem, surgeons were instructed to complete the case report forms based on their knowledge of the patient's medical condition--regardless of whether or not it appeared in medical charts (Yuan et. al, 1994). In other words, data were not required to be substantiated by clinical records. Since not all complications are noted in charts, and since complications can be easily forgotten in retrospective recollection, Yahiro remarked, "treating physicians may have the bias of optimism when recording clinical and radiological data in the medical record" (1994).

In addition to the problems of selection and recall bias, the cohort study also failed to adequately address the issue of confounding. Confounding occurs when both the exposure and the outcome are related to an additional variable that can mask the apparent affects (Hennekens & Buring, 1987). Known confounders in this study included patient gender, age, weight, prior back surgeries, and smoking habits. These are mentioned and summarily dismissed by the authors. In his review of the cohort study, Yahiro (1994) admitted that,

> "...the study data demonstrate that there were differences among treatment groups in terms of age and sex distribution, percentage of cases with prior back surgeries, number of cases with multiple involved levels, and number of cases with greater than two levels fused. The significance of these differences should be discussed further."

Perhaps even more important than these confounders are the "Yellow Flags" described by Nachemson (1995a). These flags, which include health beliefs, coping abilities, work and social environment, and insurance coverage, are highly associated with the outcomes of back surgeries and may also be associated with the types of surgeries prescribed by physicians. According to Dr. Nachemson (1995a), the predictive value of these factors is of such clear importance, and has emanated from such a large body of information, that psychosocial evaluations should be the first ones performed by physicians considering spine surgery.

A final issue in the interpretation of the cohort study is the assumption of cause and effect. This type of epidemiological study is poorly suited for determining cause and effect. In order to prove that a specific intervention caused an apparent association, three conditions must be present: (1) a strong association between the intervention and the outcome; (2) a biologically

credible explanation for the relationship; and (3) consistency with other studies (Hennekens & Buring, 1987). These conditions were not adequately met in this study: the association between pedicle screw use and beneficial outcomes is weak, the biological credibility is based on questionable assumptions of the benefits of fusion, and the study results are not consistent with the IDE data or the clinical studies discussed in the upcoming sections of this document. Thus, the associations reported in the Historical Cohort Study cannot be presumed to have been caused by the interventions.

Barely Perceptible Benefits Found

The problems with the study methods and interpretation cast severe doubts on the results achieved. But even if one accepts the procedures, the benefits of pedicle screws described in this study are small. In the spondylolisthesis group, the incremental benefit of pedicle screw use over fusion with no instrumentation was 7.6% for neurological root function, 3.7% for functional abilities (and authors report that long-term functional outcomes are even lower), 7.5% for back pain, and 3.3% for leg pain. In other words, only one out of every 13 patients receiving pedicle screws had better neurological root function and less back pain than if they had received fusion without pedicle screws. Furthermore, 27 out of every 28 patients had no better functional results using pedicle screws than they would have had with non-instrumented fusions, and 29 out of every 30 patients had no better reduction of leg pain when pedicle screws were added to fusion surgeries than they would have had without instrumentation (Yuan et. al., 1994).

In the fracture group, pedicle screws were slightly more effective than other spinal instrumentation in the resolution of neurological root function and leg pain, but they were less effective than other instrumentation in providing satisfactory functional outcomes and reduction of back pain (Yuan et.al., 1994).

Risks Encountered

These small benefits must be considered within the context of the potential risks. Patients treated with pedicle screws had significantly higher rates of re-operations than did patients who received other treatments (17.6% compared to 15.0 percent for spondylolisthesis patients, 23.4% compared to 19.4% for fracture patients). In addition, pedicle screws presented additional risks of pedicle fracture, nerve injury, and screw breakage not found with other treatments (Yuan et. al., 1994).

In summary, the Historical Cohort Study provides an insufficient basis on which to determine the safety and efficacy of pedicle screw spinal systems. The use of faulty methods precluded the acquisition of reliable data. For patients with spondylolisthesis, the study shows few, if any, benefits of pedicle screw instrumentation over fusion with no instrumentation. For patients with spinal fractures, the cohort study shows no benefits of pedicle screws in terms of functional outcomes or pain reduction compared to other types of instrumentation. In both cases, pedicle screws are associated with increased risks of complications and re-operations.

Investigational Studies

A total of 17 applications for Investigational Device Exemptions (IDEs) for pedicle screw spinal systems had been filed prior to the 1994 Orthopedic and Rehabilitation Devices Advisory Panel meeting. The data from these studies do not support the use of pedicle screws. In a 1994 affidavit in support of plaintiffs' motion for class certification, Alfred A. Rimm, Chairman of Epidemiology and Biostatistics at Case Western University of Medicine, refers to a speech given by Dr. Yahiro at the North America Spine Society annual meeting in 1993. He quotes Dr. Yahiro as saying:

> "In the last nine years, the FDA has not received valid scientific evidence demonstrating the safety and effectiveness of pedicle screws, despite the hundreds of articles in the orthopedic literature, hundreds of scientific presentations...and 14 on-going FDA-approved clinical trials....[T]he data presented in manufacturer's applications have not stood up to FDA scrutiny."

Some of the data from nine IDE studies was reformatted and presented at the Orthopedic and Rehabilitation Devices Advisory Committee Panel Meeting on July 22, 1994. These data showed that patients enrolled in the IDE studies had significantly more post-operative adverse events and instrumentation removals than were reported in the cohort studies. According to Dr. Nachemson, rather than assuming that the differences in reported outcomes between the IDE studies and the cohort study are unimportant, the FDA should interpret this as an additional signal that the cohort study could be flawed (Nachemson, 1995).

No IDE study has ever provided sufficient data to support a premarket approval application. In fact, the FDA has never approved a PMA from any pedicle screw manufacturer. In some cases, the FDA has specifically replied that data submitted do not demonstrate safety and effectiveness. According to Dr. Rimm's testimony, Dr. Beninger from the FDA also lamented the present state of affairs when he wrote the following about pedicle screws in 1993:

> "PMAs have been submitted for such patients, but FDA has refused to accept them for filing because of patient inadequacies in the applications, including insufficient follow-up of patients, statistically inadequate sample sizes, lack of defined clinical justifications for patient entry, lack of valid controls, and lack of discernable endpoints."

If the FDA has never found a clinical study sufficient to support the safety and effectiveness of pedicle screws, on what information is it now basing its proposal to down-classify these devices?

Reliable Studies of Pedicle Screw Outcomes

Most of the more than 150 published papers discussing pedicle screws are case reports of specific procedures, instrumentation, or surgeons. The results from these studies vary widely. According to 1994 affidavit testimony of Gary M. Franklin, MD, MPH, Board-certified neurologist and faculty at the University of Washington School of Public Health and Community Medicine,

> "It is my opinion to a reasonable degree of medical certainty...that the indications, efficacy, and outcome of lumbar fusion procedures have not been adequately studied, and the actual outcomes of such procedures are worse than those results which are reported."

No study with reliable methods has ever proven that pedicle screws improve the outcome of spinal fusions. A total of four prospective, randomized clinical trials of pedicle screw systems have been reported in the literature. Of these, only three are interpretable because they maintained the study protocol throughout the duration of the clinical trials. In addition, two cohort studies can be considered reliable because they used matched subjects and outside reviewers. The often-cited prospective study by Steffee and Brantigan conducted under an FDA-supported IDE is highly misleading.

The first prospective, randomized study of lumbar fusion was reported by Zdeblick in 1994. He discussed 124 patients who underwent lumbar or lumbosacral fusion for degenerative conditions. Patients were randomly assigned to treatment by either posterolateral fusion using autogenous bone graft (group I), fusion supplemented by semi-rigid pedicle screw/plate systems (group II), or fusion supplemented by rigid pedicle screw/rod fixation systems (group III). Zdeblick found an overall fusion rate of 65% for group I, 77% for group II, and 95% for group III. He reported clinical success in 71% of group I, 89% of group II, and 95% of group III. These results are uninterpretable, however, because the author broke the study protocol in nine patients. These patients, who were originally assigned to groups II or III were placed in group I intraoperatively because of severe osteopenia--a condition that rarely results in good clinical outcomes. If these patients had been included in either of groups II or III, it is likely that the success rates reported for these groups would have decreased.

Three other prospective studies appear to have satisfactory methodology. McGuire and Amundson (1993) published a report of 28 low grade spondylolisthesis patients who were randomly assigned to receive laminectomy, nerve root decompression, and posterolateral autogenous iliac crest graft fusion with either no internal fixation or with pedicle screws and plates. All patients were followed for a minimum of two years. No differences in fusion rates or clinical outcomes were found between the study populations. The authors concluded that "[w]ith the additional costs and risks associated with the use of internal fixation, routine use of hardware in this particular situation must be questioned."

Möller and Hedlund (1994) reported a second study of spondylolisthesis patients. In this study, 37 patients were randomly assigned to physical therapy, posterolateral fusion, or posterolateral fusion with pedicle screw instrumentation. Patients were followed for at least two years. The authors found that pain and functional deficits were significantly lower in patients who received fusion surgery as compared to patients who received conservative treatment, but they found no statistical differences in outcomes between patients who received pedicle screw instrumentation and those who did not.

Finally, Grob, Humke, and Dvorak (1995) reported on 45 patients who were treated for lumbar spinal stenosis without instability. Patients were randomized into three treatment groups:

decompression with laminotomy and medial facetectomy (group I), decompression and arthrodesis of the most stenotic segment using pedicle screw instrumentation (group II), or decompression and arthrodesis of all of the decompressed vertebral segments using pedicle screw instrumentation (group III). They found that all patients improved and that there were no significant differences in pain relief among the three groups. The authors concluded that in the absence of segmental instability, arthrodesis is not necessary after decompression of the lumbar spine in patients with degenerative lumbar spinal stenosis.

Two other studies are notable because they used reliable methods despite their use of retrospective design. One study matched subjects on diagnosis, previous spinal surgery, lack of litigation or workers' compensation, operating physician, and psychiatric status. Patients were categorized into four groups: posterior lateral fusions and discectomies without internal fixation (group I), fusions and discectomies with Knodt rods (group II), fusions and discectomies with Harrington rods (group III), or fusions and discectomies with VSP pedicle screw systems (group IV). The authors found that for the diagnosis of herniated disc with segmental instability and the instrumentation systems in this study, the results of spinal fusions were superior when no internal fixation was used (Zucherman, Hsu, Picetti, White, Wynne, & Taylor, 1991).

The second study compared lumbar and lumbosacral fusion with and without pedicle screw fixation for 47 patients with degenerative lumbar disease with clinical instability (Bernhardt, Swartz, Clothiaux, & Crowell, 1992). This study found that the rates of pseudarthrosis and clinical successes did not significantly differ between the two groups. Two pedicle screw patients had postoperative loss of sensation in their legs, whereas this complication was not observed in the control group. The authors concluded that bilateral posterolateral lumbar or lumbosacral fusion without internal fixation is as effective as and safer than fusion with pedicle screw instrumentation.

In summary, no reliable study has shown that pedicle screws enhance clinical outcomes in patients with spondylolisthesis, spinal stenosis, herniated disc, or degenerative lumbar disease.

A paper written by Arthur Steffee and John Brantigan (1993) entitled "The Variable Screw Placement Spinal Fixation System: Report of a Prospective Study of 250 Patients Enrolled in Food and Drug Administration Clinical Trials" has been cited as significant because it was performed under an FDA-approved protocol. The article claimed an overall fusion success rate of 93%, and overall clinical success rate of 82% with a 27% loss to follow-up.

Not only are the 27% loss to follow-up and the lack of a control group sufficient reasons to discredit this study, but affidavit testimony suggests that this clinical trial was based on incomplete and misleading data. According to Dr. Carl Larson, Ph.D., P.E., Director of the FDA Division of Surgical and Rehabilitation Devices (the division under whose jurisdiction pedicle screws fall), from October 1979 through January 1992, this is the same clinical trial that was terminated by the FDA because inspections of the investigational sites and the investigator's records revealed numerous and gross violations of the approved clinical protocol. Specifically,

the FDA found that Acromed, the IRBs, and its investigators were severely negligent in the monitoring and conduct of the clinical trials resulting in failure to maintain accurate data, failure to conduct adequate follow up on patients, failure to obtain appropriate informed consent from patients, and failure to report all adverse incidents related to the device. In addition, the patients enrolled in this IDE were only a small percentage of those actually being implanted with the device. Therefore in April of 1990, the FDA revoked Acromed's clinical trials for its VSP plates and pedicle screws, without granting the company an opportunity for a hearing, because the risk to the public health was so great.

If the FDA so mistrusted the data from this study that it revoked Acromed's IDE and terminated its clinical trials, why was this paper ever allowed to be published?

Proposal to Expand the Use of Pedicle Screw Systems

On its own accord, the FDA has proposed to down-classify pedicle screw spinal systems from class III to class II for the treatment of acute and chronic instabilities and deformities including spondylolisthesis, fractures and dislocations, scoliosis, kyphosis, and spinal tumors (Federal Register, 10/4/95). These indications for use are considerably broader than the ones endorsed by the FDA's Orthopedic and Rehabilitation Devices Panel, who proposed that pedicle screw systems be classified as class II devices only for the treatment of severe and degenerative spondylolisthesis and spinal trauma.

The FDA is proposing to make this regulatory decision without an acceptable scientific foundation. No study has proven that patients without instability need spinal fusion at all. Furthermore, clinical studies show that pedicle screws do not enhance the outcomes of spinal fusion in the treatment of mild spondylolisthesis, spinal stenosis, herniated disc, or degenerative lumbar disease. No reliable studies have even been conducted to evaluate the use of pedicle screws in the treatment of scoliosis, kyphosis, or spinal tumors.

The FDA should be very cautious about making regulatory decisions in the absence of valid data. Although it does not regulate individual physician practices, the FDA should not endorse use of devices or procedures that are not backed by solid foundations of scientific evidence.

PEDICLE SCREW SYSTEMS HAVE BEEN ASSOCIATED WITH SIGNIFICANT AND UNIQUE COMPLICATIONS THAT IMPACT FUNCTIONAL ABILITIES, COMFORT, AND THE NEED FOR ADDITIONAL SURGICAL PROCEDURES

Pedicle screws subject patients to intraoperative and post-operative events that can significantly increase complications. The FDA has consistently recognized these risks. In its determination against accepting Acromed's 510(k) notification for the VSP Spinal Fixation System, the FDA noted that the device posed potential risks not exhibited by other spinal fixation systems including: (a) a greater chance of neurological deficit due to imprecise screw placement and in the event of screw failures; (b) pedicle fracture during placement of the screw; (c) soft tissue

damage or inadequate fusion due to bending or fracture of device components; and (d) greater risk of pseudarthrosis due to instability of design (Larson, 1994).

These risks were confirmed by Robert Peyster, MD, a neuroradiologist at SUNY Medical School. Dr. Peyster has evaluated and interpreted radiographic films on thousands of patients who have undergone spinal surgeries. In affidavit testimony, Dr. Peyster reported,

> "I have repeatedly seen evidence of failed broken screw devices and failed pedicle screw surgery, many of which consisted of fractured, broken and loose pedicle screws or, malplaced/malpositioned pedicle screws with resulting pain, radiculopathy and/or neurological deficits.
>
> "It is my opinion that instrumented fusion surgeries with pedicle screws make clinical diagnosis of screw placement, nerve impingement and other soft tissue injury following surgery exceedingly difficult and often impossible, without the benefit of performing additional, extremely invasive exploratory surgery or myelography which is only helpful in diagnosing gross nerve root impingement. Even then, small transgressions of the screws outside the pedicle body may not be detected even though they may, nonetheless, be causing the patient severe neurological damage, and severe pain and symptomatology."

These risks and others have been extensively discussed in the literature. Esses, Sachs, and Dreyzin (1993) reviewed the published reports and found that the incidence of neurological complications following pedicle screw placement ranged from 0-22.5% with an average across all systems of 3.4%. Problems with screws ranged from 1-25% with an average of 9.7%. Infection ranged from 1-8% with an average of 3.6%.

In addition, Esses et. al. reported on a survey of members of the American Back Society's Committee on Surgery. Thirteen surgeons contributed data on 617 cases of pedicle screw fixation. The results of this study indicated that the rate of intraoperative complications (including unrecognized screw misplacement, pedicle fracture, CSF leak, and blood vessel injury) was 9.6%. The rate of postoperative complications (including infection, screw breakage, nerve injury, and hardware failure) was 17.8%. Consistent with previously published studies by Whitecloud, Butler, Cohen, and Candelora (1989), patients undergoing spine surgery for the first time had significantly fewer complications than those patients who had undergone previous spinal surgery.

In addition to the well-documented risks of implant failure, neurological complications, infection, and the need for additional surgery, Dr. Peyster (1994) reported a further complication of pedicle screw surgery: the preparation of the patient to receive pedicle screw implantation often leaves the spine in a weaker and more unstable state than it was prior to the surgery. He reported that the implantation of pedicle screw spinal systems is extremely invasive, involving the removal of a great deal of muscle tissue and the lamina of the vertebrae, rendering the spine and supporting structures weakened. His testimony included the following,

> "I have...seen in all of the cases of pedicle screw fusion surgery I have reviewed, wide bilateral laminectomies to facilitate hardware placement which...create vertebral instability where none existed or increase instability in those very limited cases where patients show some evidence of instability prior to surgery. The result is that if the patient doesn't have a solid fusion he/she will have gross instability and more pain" (Peyster, 1994).

Furthermore, Dr. Zdeblick, an orthopedic surgeon at the University of Wisconsin, reported the following at a recent conference on spine surgery,

> "Surgeons may want to think twice about performing instrumented fusions in heavy laborers and young active patients...[t]he extensive muscle stripping that occurs during the operation may be a cause of continuing symptoms in the physically active patient.
>
> "'Fusion disease' constitutes the symptom complex of postoperative back weakness and fatigue, and is primarily due to paraspinal muscle ischemia and denervation which occurs during the fusion procedure...[i]n a typical instrumented fusion, a long incision is made to accommodate the implant. This requires extensive stripping of the vertebral body bones. By stripping these muscles well past the tip of the transverse processes, the muscles lose blood supply and nerve supply as the posterior primary rami are disrupted. The muscles eventually heal but never regain their former level of function, even after aggressive rehabilitation.
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> "Because of the muscle damage that occurs during an instrumented fusion, surgeons should select their surgical candidates carefully...[i]n young, physically active patients, and especially in heavy laborers, the benefits of an instrumented fusion may not be as clear [as in elderly patients]....when these patients return to work, they often complain of back pain and fatigue in the afternoon. They never return to their preoperative level of work duty, and many are unable to return to their customary sporting activities" (Backletter, 1995).

PEDICLE SCREW MANUFACTURERS HAVE SHOWN BLATANT DISREGARD OF U.S. LAW AND FDA REGULATIONS BY OPENLY AND ILLEGALLY PROMOTING OFF-LABEL USE OF THESE DEVICES

Senior officials at the FDA have known about the illegal promotion and overuse of pedicle screw systems since 1985, yet no civil or criminal actions have been brought against any manufacturer. According to Dr. Larson (1994), who was intimately involved in the regulation of pedicle screw products by the FDA,

> "...[manufacturers] and the medical device industry have actively promoted pedicle screw devices in derogation of the Medical Device Amendments to the Food, Drug, and Cosmetic Act, and in reckless disregard for the fact that they have never been able to

demonstrate with scientifically valid data or evidence that these devices were safe of effective for spinal fusion surgery.

"....All of the FDA's clearance and classification decisions are based upon the intended use of the device as represented to us by the manufacturer or device proponent. If the device is promoted for a use other than that which is represented to be its intended use and which serves as a basis for Pre-Market approval or 510(k) clearance, then that device is considered misbranded or adulterated in violation of federal law.

"The FDA's position on pedicle screw devices has consistently been that these devices are significant risk Class III investigational devices which require an IDE and Pre-Market Approval. There has never been sufficient safety and efficacy data provided to allow such approval.

"As of the present date, no pedicle screw manufacturer has been able to successfully complete a clinical trial under an IDE which has led to Pre-Market Approval of any pedicle screw device. Accordingly, there are no legally marketed pedicle screw devices in this county at present, nor has there ever been any demonstrated to be reasonably safe and effective for pedicle fixation" (Larson, 1994).

The FDA's position regarding these devices was further established in a letter to the American Academy of Orthopedic Surgeons dated July 13,1993. That letter stated:

"....In this case the Medical Device Amendments are clear in language and intent. New intended uses and new [pedicle screw systems] pose a potentially significant risk to patients and are automatically classified as class III devices and may only be marketed (and promoted for new uses) after agency approval of a Pre-Market application (PMA). Since 1984 the FDA has repeatedly informed sponsors of such products of the classification status and the conditions under which these new devices could be clinically investigated to determine their safety and effectiveness. Beginning in 1988, FDA has further notified sponsors of screw and plate medical device products submitted through the 510(k) process of the classification of vertebral pedicle screws, limitations imposed on labelling, promotion and marketing for devices such as bone screws, inter-vertebral body screws, sacral screws, iliac screws, bone plates, and spinal fixation systems incorporating bone screws. These 510(k) letters now also include notice of what would constitute adulteration or misbranding of approved devices. In sum, there are no legally marketed bone plates, bone screws, spinal screws, pedicle screws, or device systems that incorporate bone screws commercially available in the United States, that have been cleared or approved for spinal fixation when used for attachment through the pedicle of a vertebra" (Larson, 1994).

Although many manufacturers have violated federal laws in promoting their devices, none have done so as flagrantly as Acromed. In 1983, Dr. Arthur Steffee patented the VSP Spinal Fixation

System. This device was commercially produced by Acromed Corporation, and designed as an internal spinal fixation device involving plates to be attached to the spine by means of the insertion of bone screws into the pedicles of the vertebrae. In September of 1984, Acromed submitted a 510(k) notifying the FDA of its intent to market the VSP Spinal Fixation System. In December of 1984, the FDA notified Acromed that the device could not be found substantially equivalent to any predicate device because of insufficient information, and offered to reevaluate the 510(k) notification if Acromed would submit additional data pertaining to safety and efficacy for its intended use. Although Acromed submitted additional information, in November 1995 the FDA notified Acromed that the device was determined to be not substantially equivalent (NSE) for its intended use and would be classified as a class III significant risk investigational device because it posed "potential risks (new types of safety and effectiveness concerns) not exhibited by other spinal fixation systems" (Larson, 1994).

In December of 1985, Acromed submitted separate 510(k) notifications for devices called the "Acromed Nested Bone Plate" and the "Cancellous Bone Screw". These devices were technologically identical to the VSP Spinal Fixation System. In January of 1986, in direct response to questioning from the FDA, Acromed responded that these bone plates and bone screws were intended for use "in appropriate fractures of long bones of both the upper and lower extremity" (Larson, 1994).

After considering Acromed's 510(k) applications for the "Nested Bone Plate" and "Cancellous Bone Screw", and in direct reliance upon Acromed's representation that the devices were intended for use solely in fractures of long bones in both the upper and lower extremities, the FDA issued a finding of substantial equivalence for these devices, and they were designated as class II devices for that specific use pursuant to 21 CFR 888.3030. As such, they were permitted to be commercially distributed for use in the long bones of the arms and legs. According to Dr. Larson, this finding could "in no way be construed as permitting use of the Acromed bone screws and bone plates in the pedicles of the spine for spinal fusion procedures. Inherent in the FDA's decision and in the classification of the device, was the limitation imposed upon us at the FDA by Acromed representing in writing that the device was intended for use solely in healing fractures of the long bones" (Larson, 1994).

Dr. Larson continued, "There can be no question that Acromed misrepresented the intended use of the device. Indeed, I have even seen testimony from Acromed's own Corporate Designee admitting that, in fact, there were no known clinical uses for these devices other than pedicle screw fixation in spinal fusion procedures, even though the devices were shipped to hospitals with appropriate packaging and labelling, limiting approved use of the devices to fixation of long bones."

In addition, there is no question that Acromed actively labeled and promoted its bone plates and screws exclusively for use in spinal fixation procedures involving the insertion of screws within the human pedicles. Among other things, Acromed published a catalog describing and depicting its bone plates and screws as "transpedicular screws" and "spine plates." Acromed encouraged spine surgeons to ignore the approved labelling and use its plates and screws in an unapproved

manner in spinal fusion procedures. Acromed rewarded the surgeons by appointing them to its Medical Advisory Board, furnishing the them with lucrative stock options through which they could participate in the financial growth of the company, and paying their expenses for attending meetings and symposia to learn the techniques of spinal instrumentation using the VSP device. Moreover, Acromed apparently prepared a booklet for spine surgeons to provide to their patients which promoted the use of VSP implants and screws in back operations. In addition, Acromed created and disseminated to physicians a "Techniques Manual" which demonstrated the use of its plates and screws exclusively in spinal pedicle fixation procedures. "Because the FDA never cleared or approved Acromed's bone plates and screws for any spinal applications, all of these activities by Acromed constituted misbranding and adulteration of the devices in violation of federal law" (Larson, 1994).

Rather than answer our call to prosecute Acromed for this violation of Federal law, the FDA instead decided to facilitate the manufacturer's continued operation. In January, 1995, the FDA determined that sufficient evidence existed demonstrating that pedicle screw spinal systems were commercially available prior to 1976. Thus, manufacturers can now obtain market approval for pedicle screw systems through the 510(k) process, rather than the much more careful and scientific premarket approval process.

Again, we must ask the FDA: Why was Acromed never prosecuted for this violation of Federal law and its blatant disregard for public safety? We again urge the FDA to pursue criminal proceedings against Acromed and against all manufacturers who conducted the same criminal practices.

THERE IS INSUFFICIENT INFORMATION TO DETERMINE WHAT TYPES OF SPECIAL CONTROLS COULD PROVIDE REASONABLE ASSURANCE OF THE SAFETY AND EFFECTIVENESS OF PEDICLE SCREW SYSTEMS OR TO ESTABLISH A PERFORMANCE STANDARD TO PROVIDE SUCH ASSURANCE

In its proposed rule issued October 4, 1995, the FDA proposed to down-classify most pedicle screw spinal systems from class III to class II. Class III and class II devices differ in the level of regulatory review performed prior to marketing. Class III devices require pre-market approval by the FDA, including clear demonstrations of safety and effectiveness; class II devices require only pre-market notification to the FDA but may be subject to device-specific special controls and/or performance standards to provide reasonable assurance of safety and effectiveness.

Class III devices are those which: (1) lack sufficient information on which to base appropriate standards of safety and effectiveness, (2) are intended to support life or prevent impairment of health, or (3) present unreasonable risks of illness or injuries. Pedicle screws meet each of these criteria. By down-classifying pedicle screws into class II, the FDA is misrepresenting the safety and effectiveness of these devices to physicians and to the American public.

Since pedicle screws have an unacceptably high rate of complications, since no unbiased studies have demonstrated their effectiveness, and since no standards have been developed to ensure their safety, pedicle screw systems must remain classified as class III devices until their safety and effectiveness are proven.

No studies have thus-far been conducted comparing the outcomes of different types of pedicle screw systems. Furthermore, no research has been published describing the physician training, operative procedure, or post-operative care that optimizes patient outcomes. These issues are vitally important in determining the types of special controls to impose on class II devices. In the absence of this information, the FDA cannot permit special controls to serve as the sole guardian of patient welfare.

There is considerable evidence that the different types of pedicle screws currently on the market result in different outcomes. Of the 64 MDR reports on pedicle screws in the past six months, 51 are from Acromed, seven are from Sofamer Danek, five are from Depuy, and one is from Zimmer. Statistical analyses of the reformatted IDE data presented at the Orthopedic and Rehabilitation Devices Advisory Panel Meeting showed that within a given diagnostic group, it was not possible to pool data across all devices--in other words, the data obtained from different devices did not produce comparable results. Zdeblick (1993) found significant differences in outcomes using rigid as compared to semi-rigid systems. Esses et. al. (1993) found the complication rate to be highly dependent on the manufacturer and type of instrumentation used and noted a ten-fold variation in outcomes between surgeons. In a review of 45 retrospective studies, Deyo (1993) reported that the success of spinal fusion surgery was dependent on patient populations, surgeons involved, and the research design methods.

From these data, it is clear that pedicle screw systems do not all result in the same outcomes. Thus, each type of device must be evaluated individually for safety and effectiveness.

Furthermore, nothing has ever been published examining the types of post-surgical surveillance that would be necessary to provide sufficient assurance that public safety would be protected. In the absence of this information, the FDA would be remiss in removing the requirement for clinical studies and allowing special controls to be the sole determinant of pedicle screw safety and efficacy.

SUMMARY

In summary, we call upon the FDA to take the following actions in regulating pedicle screw spinal systems:

1) Retain the class III classification of pedicle screws until randomized, prospective, clinical trials elucidate the benefits and risks of these devices.

2) Require manufacturers to submit acceptable premarket approval applications demonstrating their safety and effectiveness prior to marketing any further systems.

3) Classify the unclassified preamendments pedicle screw spinal system intended for the treatment of severe spondylolisthesis of the fifth lumbar vertebrae into class III.

4) Move immediately for substantial criminal or civil penalties against each manufacturer that illegally promoted the pedicle screw systems.

CONCLUSIONS

Over 350,000 patients in the United States have received pedicle screw instrumentation implanted in their spines. The majority of the recipients were not informed of the investigational nature of the devices, and the evidence is growing that a significant number of patients have suffered adverse consequences from using these systems. If the Medical Device Amendments and the FDA are to offer any protection from unproven or unsafe medical devices, medical device manufacturers and physicians must not be permitted to circumvent FDA regulations in such a manner as has occurred with pedicle screws. Essentially, the "off label" use of pedicle screws has become the only clinical use of these devices. Despite the fact that the industry has made an enormous profit, it has never been able to prove that pedicle screws are safe and effective for stabilization of the spine or reduction of clinical symptoms. Classification of pedicle screws into class II would relieve the manufacturers of ever having to prove that their devices are safe and effective, and would thus ensure that randomized clinical trials never occur.

The elimination of the requirement for clinical trials would set a terrible precedent for the FDA. According to the data presented here and elsewhere, there has thus far been insufficient evidence on which to base a decision about safety and efficacy. In the treatment of degenerative disc disease or spondylolisthesis, no well-designed study has ever proven that fusion with pedicle screws is superior to fusion without instrumentation. In the treatment of spinal fractures, no study has ever proven that pedicle screws are more effective than existing instrumentation. For other diagnoses such as scoliosis, kyphosis, or spinal tumor, there is absolutely no clinical data available. Making a significant regulatory decision to down-classify pedicle screws on the basis of bad or non-existent data will only hurt the American public and the reputation of the FDA.

Physicians have a moral obligation to provide their patients with the best available care. Many have complained that they cannot ethically undertake a controlled, randomized study because they cannot deny their patients access to state-of-the-art treatment. The data presented here answer that concern: since there is no evidence proving significant benefits of pedicle screw instrumentation, the only ethical choice is to proceed with randomized clinical intervention studies.

We must again urge the FDA to wait until all the evidence is collected before making regulatory decisions about pedicle screw classification. The data collected thus far has demonstrated that eliminating the use of pedicle screws will hurt nobody. Acting precipitously to expand the use of pedicle screws could permanently harm thousands of people.

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