Dated: July 17, 1998.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 98–19895 Filed 7–24–98; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 888

[Docket No. 95N–0176]

RIN 0910–ZA12

Orthopedic Devices: Classification and Reclassification of Pedicle Screw Spinal Systems

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is classifying certain previously unclassified preamendments pedicle screw spinal systems into class II (special controls) and reclassifying certain postamendments pedicle screw spinal systems from class III (premarket approval) to class II. FDA is taking this action because it believes that special controls would provide reasonable assurance of safety and effectiveness. This action is being taken under the Federal Food, Drug, and Cosmetic Act (the act), as amended by the Medical Device Amendments of 1976 (the 1976 amendments), the Safe Medical Devices Act of 1990 (the SMDA), and the Food and Drug Administration Modernization Act of 1997 (FDAMA).

EFFECTIVE DATE: August 26, 1998.

FOR FURTHER INFORMATION CONTACT: Aric D. Kaiser, Center for Devices and Radiological Health (HFZ–410), Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850, 301–594–2036.

SUPPLEMENTARY INFORMATION:

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I. Background

The act (21 U.S.C. 331 *et seq.*), as amended by the 1976 amendments (Pub. L. 94–295), the SMDA (Pub. L. 101–629), and FDAMA (Pub. L. 105–115), established a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the act (21 U.S.C. 360c) established three categories (classes) of devices, depending on the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are: Class I (general controls), class II (special controls), and class III (premarket approval).

Under section 513 of the act, devices that were in commercial distribution before May 28, 1976 (the date of enactment of the 1976 amendments), generally referred to as preamendments devices, are classified after FDA has: (1) Received a recommendation from a device classification panel (an FDA advisory committee); (2) published the panel's recommendation for comment, along with a proposed regulation classifying the device; and (3) published a final regulation classifying the device. FDA has classified most preamendments devices under these procedures.

Devices that were not in commercial distribution prior to May 28, 1976, generally referred to as postamendments devices, are classified automatically by statute (section 513(f) of the act) into class III without any FDA rulemaking process. Those devices remain in class III and require premarket approval, unless and until: (1) The device is reclassified into class I or II; (2) FDA issues an order classifying the device into class I or II in accordance with new section 513(f)(2) of the act, as amended by FDAMA; or (3) FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the act, to a predicate device that does not require premarket approval. The agency determines whether new devices are substantially equivalent to previously offered devices by means of premarket notification procedures in section 510(k) of the act (21 U.S.C. 360(k)) and part 807 of the regulations (21 CFR part 807).

A preamendments device that has been classified into class III may be marketed, by means of premarket notification procedures, without submission of a premarket approval application (PMA) until FDA promulgates a final regulation under section 515(b) of the act (21 U.S.C. 360e(b)) requiring premarket approval.

Reclassification of classified preamendments devices is governed by section 513(e) of the act. This section provides that FDA may, by rulemaking, reclassify a device (in a proceeding that parallels the initial classification proceeding) based upon ''new information.'' The reclassification can be initiated by FDA or by the petition of an interested person. The term ''new information,'' as used in section 513(e) of the act, includes information developed as a result of a reevaluation of the data before the agency when the device was originally classified, as well as information not presented, not available, or not developed at that time. (See, e.g., *Holland Rantos* v. *United States Department of Health, Education, and Welfare*, 587 F.2d 1173, 1174 n.1 (D.C. Cir. 1978); *Upjohn* v. *Finch*, 422 F.2d 944 (6th Cir. 1970); *Bell* v. *Goddard*, 366 F.2d 177 (7th Cir. 1966).)

Reevaluation of the data previously before the agency is an appropriate basis for subsequent regulatory action where the reevaluation is made in light of newly available regulatory authority (see *Bell* v. *Goddard*, supra, 366 F.2d at 181; *Ethicon, Inc.* v. *FDA*, 762 F. Supp. 382, 389–91 (D.D.C. 1991)), in light of changes in ''medical science.'' (See *Upjohn* v. *Finch*, supra, 422 F.2d at 951.) Regardless of whether data before the agency are past or new data, the ''new information'' on which any reclassification is based is required to consist ''valid scientific evidence,'' as defined in section 513(a)(3) of the act and § 860.7(c)(2) (21 CFR 860.7(c)(2)). (See, e.g., *General Medical Co.* v. *FDA*, 770 F.2d 214 (D.C. Cir. 1985); *Contact Lens Assoc.* v. *FDA*, 766 F.2d 592 (D.C. Cir.), cert. denied, 474 U.S. 1062 (1985).) FDA relies upon ''valid scientific evidence'' in the classification process to determine the level of

regulation for devices. For the purpose of reclassification, the valid scientific evidence upon which the agency relies must be publicly available. Publicly available information excludes trade secret and/or confidential commercial information, e.g., the contents of a pending PMA. (See section 520(c) of the act (21 U.S.C. 360j(c).)

II. Regulatory History of the Device

Consistent with the act and the regulation, FDA referred the proposed classification and reclassification of pedicle screw spinal systems to the Orthopedic and Rehabilitation Devices Panel (the Panel), an FDA advisory committee, for its recommendation on the requested classification and change in classification.

The Panel reviewed complication type and rate data present in the literature, a meta-analysis of the literature; a nationwide, retrospective Cohort study of patients treated with the devices;[1] and a review of publicly released investigational device exemptions (IDE) data from patients treated with pedicle screw spinal systems. The Panel recommended that the postamendments pedicle screw spinal systems intended to treat spinal fracture and degenerative spondylolisthesis of the thoracic, lumbar, and sacral spine, be reclassified from class III into class II.

In January, 1995, a manufacturer was able to demonstrate preamendments status for pedicle screw spinal systems intended to provide immobilization and stabilization of spinal segments as an adjunct to spinal fusion in the treatment of grades 3 or 4 severe spondylolisthesis at the fifth lumbar-first sacral (L_5–S_1) spinal level. In an April 1995, homework assignment, FDA requested that the Panel recommend a classification for this unclassified preamendments device. The Panel recommended that the unclassified preamendments pedicle screw spinal systems intended to provide immobilization and stabilization of spinal segments as an adjunct to spinal fusion in the treatment of grades 3 or 4 severe spondylolisthesis at the L_5–S_1 spinal level be classified into class II.

In the **Federal Register** of October 4, 1995 (60 FR 51946), FDA published a proposed rule to classify certain unclassified preamendments pedicle screw spinal systems (for use in certain types of severe spondylolisthesis) into class II, to reclassify certain postamendments pedicle screw spinal systems (for use in fracture and other conditions) from class III to class II, and to retain in class III other postamendments pedicle screw spinal systems. The proposed rule reflected FDA's belief that the clinical outcomes and complications described in the literature, clinical data, and MDR and MedWatch surveillance data bases,[2] described patient risks and benefits of pedicle screw spinal systems comparable to other class II spinal fixation devices and that special controls have been identified which would provide a reasonable assurance of safety and effectiveness, i.e., compliance with material standards, mechanical testing standards, biocompatibility standards, and special labeling requirements. Initially, FDA provided for interested persons to submit comments on the proposal by January 2, 1996. Subsequently, in the **Federal Register** of December 29, 1995 (60 FR 67345), FDA extended the comment period until March 4, 1996, in response to several requests for extension of the comment period.

FDA received 4,060 comments in response to the proposed rule. These comments were submitted by physicians, patients, lawyers, device manufacturers, trade associations, and other interested parties. The overwhelming majority of these comments were in favor of the proposed rule, although some comments were opposed to the proposed rule, and a few were both in favor of some aspects of the proposed rule and opposed to others.

In response to comments received on the proposed rule, FDA reanalyzed the meta-analysis of the literature, the Cohort study, and the publicly released IDE data for the indications of spinal fractures and degenerative spondylolisthesis. The reanalysis of the meta-analysis of the literature consisted of a review of the summary data and conclusions from the original, published analysis. The review of the Cohort study consisted of an audit (Ref. 1) of a structured sample of all 377 patients enrolled by 21 of the 314 participating surgeons, a reanalysis (Ref. 2) of all of the data from the audit, and a comparison to the data from unaudited surgeons. The Division of Bioresearch Monitoring (BIMO) in the Office of Compliance performed the data audit, while the Office of Device Evaluation and the Office of Surveillance and Biometrics performed the reanalyses. This audit found records were incomplete and investigators had not followed the protocol. In review of the audit, the agency concluded that the disparities and irregularities were consistent, with respect to both type and scope, with other audits of similar studies. After careful reanalysis of the potential impact of the ''problem'' records, the agency concluded that they could not account for the favorable results reported in this study.

The review of the Cohort study in the context of the audit findings yielded results that supported the safety and effectiveness of these devices. For spinal fracture, pedicle screw spinal systems presented risks and benefits that were comparable to those presented by nonpedicle screw instrumented spinal fusion. The devices used in the comparison group are class II medical devices. For spondylolisthesis, the review in the context of the audit findings described an advantage for pedicle screw spinal systems with regard to the clinical outcome parameters of fusion and improvement in neurological status when compared to noninstrumented spinal fusions. For the other parameters that were analyzed, e.g., pain, function, and reoperation rate, pedicle screw spinal systems did not always demonstrate an advantage compared to noninstrumented spinal fusion. When compared to instrumented spinal fusions, however, results among pedicle screw spinal system patients for these parameters were not statistically equivalent and not worse. Thus, FDA has concluded that the results from the review of the Cohort study are consistent with those reported in the literature and the publicly released IDE data.

The reanalysis of the meta-analysis of the literature describing experience with pedicle screw spinal systems in treating spinal fracture and degenerative spondylolisthesis found that pedicle screw spinal systems present risks and benefits that are comparable to those presented by nonpedicle screw spinal systems and noninstrumented spinal fusions. For degenerative spondylolisthesis, the reanalysis found

[1] The Cohort study was an open, nonblinded, historical Cohort study designed to recruit the maximum number of surgeons to provide clinical data on patients who had undergone spinal fusion surgery. Three hundred fourteen surgeons were recruited through announcements at professional society meetings and direct mailings to professional society memberships. Only clinical data from spinal fusion surgeries intended to treat degenerative spondylolisthesis or spinal trauma (fracture) that were performed between January 1, 1990, and December 31, 1991, were used in the analysis. This was done in an effort to maximize the number of patients with a minimum of 24 months followup. Data from 3,498 patients were collected.

[2] MDR and MedWatch data bases are two reporting systems that FDA uses to track adverse events, e.g., injuries, deaths, and device malfunctions, related to medical devices. The information consists of a combination of mandatory and/or voluntary adverse event reports from manufacturers, distributors, user facilities, healthcare professionals, as well as consumers.

that patient results with pedicle screw spinal systems were comparable to those with noninstrumented spinal fusions; it did not find a clinically significant improvement in results at followup obtained with instrumented spinal fusions over noninstrumented spinal fusions.

The reanalysis of the publicly available IDE data supports the Panel's recommendation for the classification and reclassification of pedicle screw spinal systems intended to treat spinal fractures and severe spondylolisthesis. It also supports the use of pedicle screw spinal systems when intended to provide immobilization and stabilization of spinal segments in skeletally mature patients as an adjunct to fusion for the treatment of the following acute and chronic instabilities or deformities of the thoracic, lumbar, and sacral spine: degenerative spondylolisthesis with objective evidence of neurologic impairment, fractures, dislocations, scoliosis, kyphosis, spinal tumors, and failed previous fusion (pseudarthrosis).

When all of these data are viewed in conjunction with the medical literature and the MDR and MedWatch surveillance data, no new issues relating to the safety or effectiveness of pedicle screw spinal systems are raised. Therefore, the agency has concluded that these data provide valid scientific evidence that certain special controls in conjunction with the general controls applicable to all devices, will provide a reasonable assurance of the safety and effectiveness of pedicle screw spinal systems for L_5–S_1 use and for use at other levels for the treatment of degenerative spondylolisthesis with objective evidence of neurologic impairment.

The agency also reviewed whether the Panel was properly constituted. Investigation of alleged undisclosed and unwaived conflicts of interest held by Panel members found either no omissions of current interests or omissions of minor interests for all but one of the Panel members. The agency has concluded that the minor omissions are insignificant and do not constitute a financial conflict of interest that would credibly influence the members' actions in forming the Panel's recommendations.

The agency has found that one voting Panel member did have significant undisclosed financial conflicts. However, because the recommendation of the Panel, both in the July 23, 1994, meeting and on the subsequent homework assignment, was unanimous and this individual was not controlling, or unduly influential, of the votes of the other Panel members and was not necessary to constitute a quorum, after expunging the participation of this Panel member, FDA has concluded that this Panel, both in the meeting and on the subsequent homework assignment, was a valid scientific Panel to make recommendations to the agency.

The agency's reanalysis of these data has confirmed its original conclusion, reflected in the proposed rule, that the risks and benefits of pedicle screw spinal systems are comparable to those of other class II spinal fixation devices. FDA's decision to classify and reclassify these devices into class II is based upon valid scientific evidence establishing that the special controls described above, along with the general controls applicable to all devices under the act, provide a reasonable assurance of the safety and effectiveness of pedicle screw spinal systems.

III. Summary of the Final Rule

In this final rule, FDA is classifying into class II the unclassified preamendments pedicle screw spinal systems intended for treatment of severe spondylolisthesis (grades 3 and 4) of the L_5–S_1 vertebra in skeletally mature patients receiving fusion by autogenous bone graft having implants attached to the lumbar and sacral spine with removal of the implants after the attainment of a solid fusion. In addition, FDA is reclassifying into class II the postamendments class III pedicle screw spinal systems intended to provide immobilization and stabilization of spinal segments in skeletally mature patients as an adjunct to fusion in the treatment of the following acute and chronic instabilities or deformities of the thoracic, lumbar, and sacral spine: Degenerative spondylolisthesis with objective evidence of neurologic impairment, fracture, dislocation, scoliosis, kyphosis, spinal tumor, and failed previous fusion (pseudarthrosis). Pedicle screw spinal systems intended for any other uses are considered postamendments class III devices for which premarket approval is required. The following four special controls apply to the devices being classified and reclassified into class II: (1) Compliance with materials standards, (2) compliance with mechanical testing standards of performance, (3) compliance with biocompatibility standards, and (4) adherence to labeling requirements.

IV. Proposed Rule Clarifications

FDA is taking this opportunity to clarify that neither well-controlled investigations nor valid scientific evidence relating to pedicle screw spinal systems intended for use in the cervical spine is available and, therefore, the safety and effectiveness of these devices for this intended use have not been demonstrated. As a result, pedicle screw spinal systems intended for use in the cervical spine are excluded from this classification and reclassification and are considered postamendments class III devices for which premarket approval is required.

In addition, although not specifically stated in the preamble to the proposed rule, all valid scientific evidence reviewed by the Panel and FDA were obtained from skeletally mature populations. To date, the safety and effectiveness of pedicle screw spinal systems in pediatric populations have not been demonstrated. Consequently, pedicle screw spinal systems intended for use in pediatric populations are postamendments class III devices for which premarket approval is required.

V. Analysis of Comments and FDA's Response

A. Issues Relating to the Recommendations of the Panel, FDA's Tentative Findings, and Summary of the Data Upon Which FDA's Findings Were Based

1. Several comments believed that valid scientific evidence was not presented to the Panel or used in formulating the proposed rule. These comments argued that only prospective, randomized, concurrently-controlled clinical trials constitute valid scientific evidence and that anything else is insufficient to support device reclassification.

FDA disagrees that only data from prospective, randomized, concurrently-controlled clinical trials can constitute valid scientific evidence. Although prospective, randomized, concurrently controlled clinical trials have the potential to produce the most convincing and reliable data, e.g., all sources of bias have been reduced to a minimum, such clinical trials are not the only type of study that can produce data adequate to support a determination that there is reasonable assurance that a device is safe and effective for its conditions for use. In fact, § 860.7(c)(2) defines valid scientific evidence as

> * * * evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under

its conditions of use. The evidence may vary according to the characteristics of the device, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use * * *.

From this definition, it is clear that there is a hierarchy of data that fits the definition of valid scientific and that, while well-controlled, prospective clinical trials are at the top of the hierarchy, they are not the only source of data that may support a determination regarding reasonable assurance of safety and effectiveness for purposes of classifying and/or reclassifying a device.

FDA also disagrees that valid scientific evidence was not presented to the Panel or used in support of the proposed rule. The three sources of data presented to the Panel and used in support of the proposed rule were: (1) Reformatted IDE data, (2) a meta-analysis of the literature, and (3) the Cohort study. The reformatted IDE data represent data from well-controlled investigations, while the meta-analysis of the literature and the Cohort study represent studies and objective trials without matched controls or well-documented case histories or reports of significant human experience. All three sources of data used in support of the classification and reclassification of pedicle screw spinal systems clearly fall within the definition of valid scientific evidence in § 860.7(c)(2).

2. One comment objected that, in addition to not being valid scientific evidence, the three sources of data, i.e., the meta-analysis of the literature, the reformatted IDE data and the Cohort study, were flawed.

The comment noted the following deficiencies with the meta-analysis:

- FDA previously determined that the available literature on pedicle screw spinal systems could not be used to support device reclassification.

FDA disagrees. FDA made that statement prior to January, 1993, when no adequate analysis of pedicle screw literature had been provided to the agency. FDA believes that, while individual literature articles describing the use of pedicle screw spinal systems would be insufficient to support reclassification of a device, group analysis of relevant articles may be adequate, especially where, as here, the group analysis is considered in conjunction with other supporting data. Furthermore, after noting the limitations of the individual studies reported in the literature, FDA concluded that the literature, taken as a whole and used in conjunction with the other sources of data, provided adequate information to support the reclassification of pedicle screw spinal systems intended to treat degenerative spondylolisthesis with objective evidence of neurologic impairment or spinal trauma.

- The meta-analysis is not an appropriate scientific technique, as applied to retrospective studies, because different studies have different parameters, biases, and strengths and weaknesses, all of which invalidate the pooling of data.

FDA disagrees. Although meta-analysis of literature may be less rigorous than other forms of scientific research, it still provides useful information. As discussed in section V.A.1 of this document, § 860.7(c)(2) defines ''valid scientific evidence'' to include many types of evidence of varying degrees of scientific rigor, including meta-analysis of literature. FDA participated in the development of the meta-analysis because the agency believed that this analysis could produce data meeting the definition of valid scientific evidence. Finally, the inherent limitations of a literature meta-analysis were discussed during the presentation of this analysis at the July 23, 1994, Panel meeting and in the preamble to the proposed rule (60 FR 51946).

- The meta-analysis actually lent support to the conclusion that pedicle screw fixation is less effective than other methods of treating degenerative spondylolisthesis and spinal fracture and that it may present the patient with more risks.

FDA disagrees. With respect to degenerative spondylolisthesis, there was no statistically significant difference in fusion rates between the control and the pedicle screw spinal system treatment groups. This is supportive data that clarifies the relative safety and effectiveness of pedicle screw spinal systems for this use. With respect to spinal fracture, significantly higher fusion rates were achieved in the pedicle screw spinal system treatment group than in the nonpedicle screw treatment groups. Thus, the meta-analysis confirmed the comparability of pedicle screw spinal systems to other class II devices used to treat spinal fracture in terms of safety and effectiveness.

- Fifty-five of the 58 studies in the meta-analysis were nonexperimental case-series having no validity as scientific evidence.

FDA disagrees. As discussed in section V.A.1 of this document, § 860.7(c)(2) states that valid scientific evidence may include ''* * * well-documented case histories conducted by qualified experts * * *''. Moreover, these well-documented case studies, which were conducted by qualified experts, were not the sole basis for the proposed classification/reclassification, but rather were considered in conjunction with data from various other sources.

The comment also noted the following deficiencies with the reformatted IDE data:

- The reformatted IDE data are not appropriate for classifying and reclassifying pedicle screw spinal systems because FDA previously had determined that these data could not support PMA's for these devices.

FDA disagrees in part. Prior to the August 20, 1993, Panel meeting, FDA had determined that data from individual IDE's were insufficient to support PMA's for those devices. Nevertheless, FDA recognized that the IDE data could still be valuable. In 1993, after receiving permission from nine IDE sponsors to publicly release and use their combined data, FDA determined that the data, reviewed as a whole, corroborated the results of other available data sets demonstrating the safety and effectiveness of pedicle screw spinal systems.

- The reformatted IDE data are inherently suspect because they (1) were reformatted by the sponsors and not by FDA, (2) were not provided for public scrutiny during the Panel meeting or at any other time, and (3) may have omitted poor results.

FDA disagrees that the reformatted data were suspect because they were reformatted by the sponsors and not by FDA. If IDE data are not properly formatted, FDA requests the sponsor to reformat its data for proper presentation to the agency. Furthermore, data in all marketing applications are formatted by the sponsor. Therefore, the simple fact that the IDE data were reformatted by the sponsor, not by FDA, does not make these data inherently suspect.

FDA also disagrees that the data were suspect because they were not presented for public scrutiny. For reclassification purposes, the valid scientific evidence upon which the agency relies must be publicly available § 860.5(e) (21 CFR 860.5(e)). Publicly available information excludes trade secret and/or confidential commercial information (21 CFR 20.61). IDE data typically contain trade secret and/or confidential commercial information and, consequently, ordinarily may not be publicly disclosed by the agency to support reclassification of a device (49 FR 17523 at 17531 and 17532, April 24, 1984). In fact, under § 812.38(a) and (b)(3) (21 CFR 812.38 (a) and (b)(3)), FDA generally does not acknowledge the existence of an IDE or disclose any

of the collected data. However, on August 13, 1993, after receiving permission from nine IDE sponsors to publicly release and use their combined data, the Commissioner of Food and Drugs (the Commissioner) exercised his discretionary authority under § 812.38(b)(2) and publicly released the data from nine IDE's, redacted of the identification of the IDE sponsors, institutional review boards, investigators, and patients. Although FDA did not make publicly available the unformatted data from the IDE studies or the identification of the IDE sponsors, institutional review boards, investigators or patients, the agency did provide the public with a detailed report of the combined IDE data (60 FR 51946 at 51961, ref. 173). This information was publicly available for analysis for more than 2 years before the publication of the proposed rule.

Finally, FDA disagrees that the data were suspect because they may have omitted poor results. Nine of fourteen sponsors provided their reformatted IDE data for analysis. There is no evidence that the five sponsors who did not offer their data did so because the data reflected adversely on the performance of their products. They may not have provided their data for any number of reasons. For instance, the sponsors may have believed that they had an inadequate amount of data to contribute to the effort or that the data may not have been in a readily accessible format. Regardless of the reason, the publicly available reformatted IDE data corroborate the results of other studies that demonstrate the safety and effectiveness of pedicle screw spinal systems. Specifically, the fusion rates, complication rates, and reoperation, revision, and removal rates attained under publicly available IDE studies were consistent with what was observed in the literature for such devices.

- The 12-month followup time period was inadequate to support any conclusions. Specifically, the comment stated that the Panel was not supplied with any information on the safety and effectiveness of these devices at more than 1 year following surgery. The comment continued that, without a minimum followup period of 2 years, it is impossible to make appropriate conclusions with regard to the longer-term safety and efficacy of these devices in accordance with accepted scientific convention.

FDA agrees that a 12-month followup time period would be inadequate and, therefore, selected a 24-month followup period for analysis. The 24-month followup period was also supported by the Panel and the literature. Contrary to the comment's statement, the Panel was supplied with information on the safety and effectiveness of pedicle screw spinal systems at more than one year following surgery. Spinal fusion generally occurs within 6 to 18 months after surgery. The majority of post-operative complications occur by the 18th month time point. For these reasons, FDA concluded that a 24-month followup period was adequate. FDA recognizes that not all of the reformatted IDE data were from a 24-month followup examination. However, a sufficient amount of data from a 24 month followup evaluation was examined for the Panel to make a recommendation about the reasonable assurance of safety and effectiveness of pedicle screw spinal systems for their class II intended uses.

- The comment stated that the lost-to-followup rate was too high.

FDA agrees that the lost-to-followup rate was high. FDA believes that patients with poor results tend to either return to their surgeons more frequently or go to other caregivers, attempting to receive the pain relief and return of function that they were originally seeking. It cannot be determined whether the patients who were lost-to-followup had acceptable results or went to other caregivers. However, FDA does not believe that this theoretical weakness in the data is of such a magnitude as to justify rejecting the studies. Thus, both the Panel and FDA believe that the lost-to-followup rate was not unacceptably high.

The comment noted the following deficiencies with the Cohort study:

- The Cohort study did not constitute valid scientific evidence.

FDA disagrees. As described above, valid scientific evidence encompasses a wide variety of data. The Cohort study satisfies the definition of valid scientific evidence because it consisted of data from well-documented case histories conducted by qualified experts and reports of significant human experience.

- The sample size and statistical power used in designing the Cohort study were inadequate and, therefore, no reliable conclusions can be drawn from the study. Another comment attempted to rebut this allegation.

FDA believes that the sample size and statistical power calculations that were performed in the Cohort study were accurate and appropriate and, consequently, that the conclusions drawn from the study had a sound basis.

- The Cohort study was biased and the data were not independently audited.

FDA disagrees. While the potential for bias exists in any study, it was of particular concern in the design of the Cohort study due to its retrospective nature. As described at the July 22, 1994, Panel meeting and in the preamble to the proposed rule (60 FR 51946 at 51954), various steps were taken to minimize the potential effects of bias due to the study design. In addition, contrary to the comment's assertion, there was a review of the data by an independent auditor and a subsequent FDA BIMO audit and review. The review by the independent auditor was not extensive and no definitive conclusions can be drawn from its analysis of the Cohort study data. Although both audits uncovered instances of protocol departures, recordkeeping inconsistencies, or a lack of clear understanding or unfamiliarity with the protocol requirements on the part of a participating surgeon, these inconsistencies and protocol departures did not affect the reliability of the data. For example, one type of reported protocol recordkeeping departure was that some data forms were incomplete. In some instances, the data forms simply omitted the patient's weight, but not the patient's fusion status. The absence of that piece of information, while rendering the form incomplete, clearly did not affect the clinical outcome analysis. A more significant protocol departure related to the inclusion and analysis of data from patients whose diagnosis did not meet patient eligibility criteria. However, no obvious pattern that would improve overall patient outcomes was identified because these departures included indications for surgery both more and less severe than those targeted by the protocol.

The data retrieved from the BIMO audit were analyzed to determine if the major outcomes of the Cohort study were significantly different (statistically or clinically) with or without the presence of protocol departures, with or without the presence of recordkeeping inconsistencies, or at sites where the participating investigator, based on the audit, was or was not familiar with the protocol requirements. While some differences were noted between sites with and without inconsistencies, in most cases, these were not statistically significant and no consistent or clinically relevant patterns were noted. The analysis of the audited data did not find systemic bias in either the conduct of the study or its reported results. None of the analyzed audit data contradicted the published results of the Cohort study. Finally, the data audit analysis concluded that the audited data were consistent with other publicly available

data and that the Cohort study data could be used as part of a larger body of data to support the classification and reclassification of pedicle screw spinal systems.

- Documents relating to the Cohort study were destroyed.

FDA disagrees. All Cohort study data were maintained in a master file. Only extra copies of information were destroyed in an effort to maintain the confidentiality of the identities of the participating surgeons and their patients. In addition, as a matter of course, FDA routinely assists Panel members in destroying copies of documents containing trade secret and/or confidential commercial information that they have received from FDA as preparatory material for a Panel meeting.

- Certain FDA employees had inappropriate relationships with pedicle screw manufacturers and others involved in the Cohort study.

This allegation, which has two parts, is unfounded. FDA performed an internal affairs investigation of the employees about whom allegations were made. This investigation showed that their attendance at a health professional meeting was properly paid for by the agency, not subsidized by the regulated industry. Also in the case of one employee, FDA's investigation showed that negotiations regarding outside employment with the regulated industry had been properly reported to the employee's supervisors and immediate colleagues in all instances.

- The Scientific Committee and the Spinal Implant Manufacturers Group (SIMG) were not independent.

FDA disagrees. The preamble to the proposed rule and the subsequent correction (60 FR 51946 and 60 FR 66227, December 21, 1995) described the makeup of the Scientific Committee and SIMG. SIMG consisted of representatives of manufacturers who provided funding to support a nationwide analysis of clinical data relating to pedicle screw spinal systems. SIMG did not participate in the design of the study. The study was designed and implemented by the Scientific Committee with input from FDA as to the feasibility of various clinical study design parameters. The Scientific Committee was formed by five professional medical societies. Although two SIMG representatives were part of the Scientific Committee, they were nonvoting members. Furthermore, even if there were not independence between the Scientific Committee and SIMG, there is no requirement that clinical studies be performed by parties independent of device manufacturers. In fact, FDA routinely receives and relies upon studies performed by manufacturers.

3. Several comments contended that financial conflicts of interest were present in the three sources of data relied on by FDA to support the classification/reclassification of pedicle screw spinal systems. The comments claimed that, in the meta-analysis of the literature, the authors of the individual articles had financial conflicts of interest due to their relationships with device manufacturers. With respect to the analysis of the reformatted IDE data and the Cohort study, the comment stated that the IDE investigators and Cohort study participants had significant financial interests in the companies whose devices they were using and, therefore, had a strong financial incentive to report only successful results. Similar objections were raised about the authors of the 206 articles cited as constituting the body of medical literature bearing on pedicle screw fixation. The comments stated that almost all of the surgeons who authored these articles failed to disclose their financial connections to manufacturers. The comments stated that such interests raise serious concerns about researchers' motivation to perform the research, the propriety and importance of research questions and research designs, the adequacy of protection of human subjects, lack of bias, and veracity in collecting and analyzing the data and reporting the results.

FDA recognizes that some of the clinical investigators involved in the three sources of data, as well as some of the authors of the 206 literature articles used to support classification and reclassification of pedicle screw spinal systems, had financial interests in the devices they were studying. FDA disagrees, however, that these financial interests resulted in biased or unreliable data. Regardless of the source of the data, the meta-analysis, the reformatted IDE data, the Cohort study, or the collection of cited literature, the conclusions were similar, i.e., that pedicle screw spinal systems are safe and effective for the uses examined. Because of this, even if financial conflicts of interest were present, they did not affect the resulting data and the conclusions. Moreover, the agency has concluded that, despite the failure to disclose the financial interests of clinical investigators, the sponsors of these investigations and/or articles took reasonable steps to minimize potential bias.

Furthermore, the fact that some spine surgeons were compensated by industry for research or consulting services, or were reimbursed for expenses incurred in connection with continuing medical education courses, did not affect the validity of any of the data. Moreover, many of the grants to support research were made directly to university accounts for general research and development, not directly to individual investigators. Consequently, the existence of a financial relationship between some surgeons and manufacturers did not necessarily result in biased case selection or reporting. Finally, FDA notes that research used to support a medical device marketing application has always been supported by the sponsor of the device and there is neither an expectation of nonsupport nor a requirement of disclosure of such support.

4. Several comments stated that pedicle screw spinal systems present different safety and effectiveness issues than do either class II spinal devices using hooks and/or wires or noninstrumented spinal fusions. One comment identified the following areas of concern as having the potential of presenting unreasonable danger for patients:

(1) Difficulty in placing screws completely within the walls of the pedicle;

(2) Inability to determine screw placement postoperatively using radiographic techniques;

(3) Damage to nerve tissue as a result of transient contact with a screw during screw placement;

(4) Nerve root damage (irritation or compression) as a result of screw malposition;

(5) Device failure;

(6) Loss of bone density as a result of stress shielding;

(7) Foreign body tissue response;

(8) Crevice corrosion;

(9) Fretting corrosion;

(10) Fibrosis;

(11) Bone fracture, particularly that of the pedicles;

(12) Nerve root or spinal cord compression as a result of fibrosis or foreign body tissue response;

(13) Chronic irritation;

(14) Spine destabilization possibly leading to nonunion;

(15) Increased venous pressure as a result of blocked venous channels within the bone;

(16) Increased risk of infection;

(17) Loss or decrease of sensory and/or motor function;

(18) Loss of bowel or bladder control; and

(19) Loss of sexual function.

FDA agrees that pedicle screw spinal systems have some potential risks that

are different from those of other class II spinal devices. However, the majority of the potential risks presented by these devices, e.g., bone fracture, foreign body tissue response, loss or decrease in sensory and/or motor function, and device failure or corrosion, are also associated with class II spinal devices which use hooks and/or wires for the same intended uses. Similarly, potential risks such as nonunion and instability are also associated with noninstrumented spinal fusions. Moreover, as described in the proposed rule, the incidence of these adverse outcomes is no greater when a pedicle screw spinal system is used than when other types of spinal fusions, instrumented and noninstrumented, are performed in appropriately selected patients (60 FR 51946 at 51957). Finally, FDA believes that the potential risks that are unique to pedicle screw spinal systems, e.g., difficulty in placing screws completely within the walls of the pedicle, inability to determine screw placement postoperatively using radiographic techniques, damage to nerve tissue as a result of transient contact with a screw during screw placement, and nerve root damage (irritation or compression) as a result of screw malposition, can be adequately addressed by the identified special controls and proper surgeon training and surgical technique.

5. One comment asserted that the supposed advantages of pedicle screw spinal systems are largely theoretical. The comment stated that, while some investigators have shown that instrumented fusions increase the likelihood of obtaining a solid fusion, others have demonstrated that there is no significant increase in fusion rates performed with instrumentation as compared with noninstrumented fusions performed with bone graft alone.

FDA agrees that the data do not always support the theoretical advantages of using pedicle screw spinal systems compared to alternate methods of achieving spinal fusion. However, in forming its recommendations, neither FDA nor the Panel is required to analyze the theoretical behavior of a given device. It is only required to determine whether the data demonstrate that there is a reasonable assurance of safety and effectiveness for its intended uses.

6. The same comment stated that spinal fusion surgery is usually performed because of the belief that spinal instability results in pain. The clinical indicators used to determine which patients have spinal instability and, therefore, are candidates for spinal fusion surgery, are not clearly defined and are often not measurable. Because the results of spinal fusion surgery are also dependent on measurements of instability, a determination of success is difficult, if not impossible.

FDA agrees that the methods used to measure instability are not perfect and that several working definitions of instability exist. Nevertheless, instability is measurable. In addition, the same instability definitions and measurement techniques are used in determining how a patient is to be treated, i.e., with pedicle screw spinal systems, class II spinal devices using hooks and/or wires, or noninstrumented fusions. FDA agrees that the determination of success of spinal fusion surgery is often difficult, but disagrees that it is impossible to determine. In fact, the success rates from using the three treatment methods described above have been determined and found to be reasonably equivalent (60 FR 51946 at 51954).

7. Three comments questioned the most appropriate classification for pedicle screw spinal systems. One comment proposed that pedicle screw spinal systems be classified into class I and two comments suggested placing them in class III.

FDA disagrees. Based on the available information, both the Panel and FDA concluded that general controls alone are not sufficient to provide a reasonable assurance of the safety and effectiveness of pedicle screw spinal systems intended to provide immobilization and stabilization of spinal segments as an adjunct to fusion in the treatment of the following acute and chronic instabilities or deformities of the thoracic, lumbar, and sacral spine: Degenerative spondylolisthesis with objective evidence of neurologic impairment, fractures, dislocations, scoliosis, kyphosis, spinal tumors, and failed previous fusion attempts (pseudarthrosis). The Panel and FDA also concluded that premarket approval was not necessary to provide such assurance. Both the Panel and FDA identified the potential risks associated with the use of these devices and concluded that sufficient information exists to establish special controls to provide reasonable assurance of their safety and effectiveness. As a result, FDA is classifying and reclassifying these devices in class II.

8. A comment believed that classification and reclassification of pedicle screw spinal systems into class II is inappropriate because FDA was correct in its prior determination that basic principles of physiology, anatomy, biology, and biomechanical engineering demonstrate that pedicle screw spinal systems present a serious risk of injury to the spinal nerves, nerve roots, and surrounding vascular structures, and increase the risk of pseudarthrosis. According to this comment, these risks are not posed by existing spine fusion technology and pedicle screw spinal systems are of questionable efficacy in comparison to existing methodologies of treatment.

FDA disagrees. FDA did not determine that basic principles of physiology, anatomy, biology, and biomechanical engineering demonstrate that pedicle screw spinal systems present a serious risk of injury. Rather, in 1984, FDA determined that a multiple component device system intended for attachment to the spine via the pedicles was not substantially equivalent to any legally marketed predicate device, in accordance with section 513(i)(1) of the act. FDA's decision was based on the fact that: (1) The sponsor did not identify a legally marketed preamendments device incorporating pedicle screw components and (2) the device posed potential risks not exhibited by other legally marketed predicate spinal fixation systems, such as a greater chance of neurological deficit due to imprecise screw placement or the event of a screw failure; pedicle fracture during placement of screws; soft tissue damage or inadequate fusion due to bending or fracture of device components; and greater risk of pseudarthrosis due to instability of the device design (60 FR 51946 at 51947). As stated previously, FDA believes that the risks to health presented by pedicle screw spinal systems intended to provide immobilization and stabilization of spinal segments as an adjunct to fusion in the treatment of the following acute and chronic instabilities or deformities of the thoracic, lumbar, and sacral spine: Degenerative spondylolisthesis with objective evidence of neurologic impairment, fractures, dislocations, scoliosis, kyphosis, spinal tumors, and failed previous fusion (pseudarthrosis) can be adequately addressed by special controls. Consequently, FDA is classifying and reclassifying these devices into class II.

9. One comment argued that manufacturers of pedicle screw spinal systems are seeking to have FDA down classify the device into class II because the manufacturers are unable to prove that pedicle screws are safe and effective for posterior implantation into the spine.

FDA disagrees. First, contrary to the comment's statement, this classification and reclassification proceeding was

initiated by FDA; it is not in response to a petition for reclassification. Second, under section 513 of the act, devices are classified/reclassified into one of three classes based on reasonable assurance, not ''absolute proof,'' of their safety and effectiveness. Contrary to the comment's statement, it was not pedicle screw spinal system manufacturers, but rather the Panel and FDA, that concluded that pedicle screw spinal systems should be classified and reclassified into class II because they determined that premarket approval is not necessary to provide reasonable assurance of the device's safety and effectiveness, general controls alone are insufficient to provide such assurance, and there is sufficient information to establish special controls to provide such assurance.

10. According to another comment, by classifying and reclassifying pedicle screw spinal systems into class II, FDA is acknowledging that there is no need for the manufacturers of pedicle screw spinal systems to prove that the devices are safe and effective.

FDA agrees. The agency has determined that sufficient information exists to establish special controls to provide reasonable assurance of the safety and effectiveness of pedicle screw spinal systems intended to provide immobilization and stabilization of spinal segments in skeletally mature patients as an adjunct to fusion in the treatment of the following acute and chronic instabilities or deformities of the thoracic, lumbar, and sacral spine: Degenerative spondylolisthesis with objective evidence of neurologic impairment, fracture, dislocation, scoliosis, kyphosis, spinal tumor, and failed previous fusion (pseudarthrosis). FDA has determined that premarket approval is not necessary to provide such assurance.

B. Issues Relating to Information Published in the 1994 Supplementary Issue of the Journal Spine (vol. 20S, 1994)

11. One comment objected that the manner in which the Scientific Committee communicated to the public the results of the Cohort study and related meta-analyses of the literature lacked scientific integrity. According to the comment, the articles were not peer reviewed, but rather they were accepted for publication solely by the Editor-in-Chief of the peer-reviewed journal Spine. The comment contended that publication of the articles without peer review prevented the studies from being submitted to the usual critical scrutiny of any peer review in the future.

While the articles describing the Cohort study and related meta-analysis were not peer-reviewed in the usual manner, they were subjected to a review process and published in an October 19, 1994, Special Supplement of *Spine*. The editorial at the beginning of the supplement states that,

> The members of the Scientific Committee and editors of *Spine* felt it important that presentations from the (July 1994, Panel) meeting be available to the readers of *Spine* in an expedited manner. The articles have been reviewed by the Scientific Committee, but have not gone through the normal review process of the Spine Editorial Board. However, it has been prepared, written, re-written, and critiqued by all members of the Scientific Committee and member of the Spine Editorial Board, as well as presented in an open public forum to the scientists who comprised the Orthopedic and Rehabilitation Devices Advisory Panel to the FDA. Weaknesses and strengths of the studies are readily apparent and have been addressed by each author, as well as in my summation.

12. The comment also stated that the articles should not have been accepted for publication because the editorial policy of the journal requires that the recommended minimum followup period for studies should be 24 months.

FDA disagrees. Under *Spine* policy, a sufficient length of time for followup of articles is necessary for publication. While the recommended time period for surgical procedures is 2 years, the policy does not state that studies with less than 2-year followup will not be published.

C. Issues Relating to the January 1995, 510(k) Substantial Equivalence Determination for a Pedicle Screw Spinal System Intended for Severe Spondylolisthesis

13. A comment stated that the circumstances surrounding the first 510(k) clearance of a pedicle screw spinal system in January 1995, were highly suspect because, until that time, FDA consistently had found bone screws for use in the pedicles to be not substantially equivalent to the identified predicate device, the lag screws used by Dr. Harrington. The comment also stated that the lag screws were manufactured as a custom device and used under a funded research grant and, therefore, were not in commercial distribution prior to 1976.

FDA disagrees. The 510(k) applicant provided new evidence documenting, for the first time, that: (1) A medical device company had manufactured and shipped in interstate commerce bone (lag) screws intended for use in the pedicles of the spine prior to May 28, 1976; (2) the devices were marketed to physicians, including, but not limited to, Dr. Harrington; and (3) the devices were not used solely for research purposes.

14. The same comment also argued that the two devices had different technological characteristics because the lag screws attach to fixation constructs by wires whereas the pedicle screws attach directly to plates or rods. The comment concluded that the applicant could not demonstrate that its device did not raise different questions of safety and effectiveness compared to the predicate device because the lag screws were used on an extremely limited basis and were abandoned because of a lack of effectiveness.

FDA disagrees. The presence of technological differences does not preclude a finding of substantial equivalence under section 513(i) of the act. In accordance with section 513(i)(1)(A)) of the act and § 807.100(b)(2)(ii)(B), for purposes of determining substantial equivalence, manufacturers have to demonstrate that their device (1) Has the same intended use as a predicate device and (2) if it has different technological characteristics than the predicate device, that the device is as safe and as effective as a legally marketed device, and it does not raise different questions of safety and effectiveness. The relative extent of use of one device compared to another is not relevant.

In making its decision, FDA analyzed all of the data provided by the sponsor. This included reports describing the clinical and mechanical behavior of the device, in addition to affidavits. From these data, the Panel and FDA determined that the complications were similar to those of a predicate device and that the technological differences raised no new questions relating to safety or effectiveness.

15. The comment also stated that FDA's reversal of its position with regard to the preamendments status of pedicle fixation devices was insupportable and a clear violation of its own regulations. Specifically, the comment stated that the agency took the unprecedented step of determining the existence of commercial distribution based solely on the affidavit of a former employee of a pedicle screw manufacturer. According to the comment, this was not sufficient evidence to demonstrate that the device was in commercial distribution prior to 1976.

The use of affidavits to document the preamendments status of a predicate device is not unprecedented. In fact, FDA routinely allows affidavits to be used to document the preamendments status of a device. FDA recognizes that obtaining labeling, advertising, and

other records concerning the marketing status of a device dating back more than 20 years is often difficult, if not impossible. Therefore, FDA allows sponsors to rely on alternative methods to demonstrate interstate commerce. Moreover, contrary to the comment's statement, the preamendments status of the device was established by much more than a single affidavit. In fact, the 510(k) submission contained several affidavits from individuals other than the sponsor, correspondence, and other documents, e.g., shipping documentation, that demonstrated the preamendments status of the Harrington lag screws for use in a limited area of the spine, i.e., L_5–S_1, and for a particular indication, i.e., severe spondylolisthesis.

16. Finally, the comment alleged that FDA changed its regulatory position regarding pedicle screw spinal systems after it made a ''deal'' with the affected industry on or about June 15, 1993. The comment stated that, if manufacturers funded a retrospective study, FDA provided assurances that it would (1) Refrain from taking criminal, regulatory, or other legal actions against them; and (2) reclassify pedicle screw spinal systems without requiring prospective studies and without regard to the quality of any of the retrospective data.

FDA disagrees. Prior to its January 1995, 510(k) decision and the publication of this classification and reclassification regulation, FDA consistently maintained that pedicle screw spinal systems, except when intended for a very limited use, were class III devices requiring premarket approval. The purpose of FDA's meeting with the affected industry and the orthopaedic professional societies was to request that these groups submit to the agency all available clinical data on the performance of pedicle screw spinal systems. FDA, at no time, agreed to change the regulatory status of these devices without regard to the quality of the data or to refrain from taking regulatory action if a retrospective study were funded.

D. Issues Relating to Misstatements or False Statements Appearing in the Proposed Rule

17. One comment alleged that the statement in the preamble to the proposed rule regarding the conclusion of the August 20, 1993, Panel meeting, i.e., that pedicle screw spinal systems appear to be safe and effective when used as adjuncts to spinal fusion procedures, was inaccurate.

FDA disagrees. The description of the August 20, 1993, Panel meeting contained in the preamble to the proposed rule states that the Panel concluded that mechanical testing data demonstrated that pedicle screw spinal systems exhibit adequate mechanical strength, rigidity, and fatigue resistance (60 FR 51946 at 51948).

18. The same comment alleged that neither the transcripts from the two Panel meetings, nor the summary in the preamble to the proposed rule accurately reflected the Panel's conclusions regarding potential risks to health associated with the use of the pedicle screw spinal system, special controls, development of performance standards, mechanical performance of the device, and the Panel members' own personal knowledge of, and clinical experience with, the device.

FDA disagrees that the transcripts of the two Panel meetings did not accurately reflect the Panel's conclusions. The proceedings from the two meetings were verbatim stenographic transcripts of oral testimony prepared by an independent transcriptionist. FDA also disagrees that the preamble to the proposed rule did not accurately reflect the Panel's conclusions. The preamble to the proposed rule mirrors the transcripts of the meetings.

19. The same comment alleged that the Panel members (voting members and voting/nonvoting consultants), who met July 23, 1994, had inappropriate relationships, e.g., financial arrangements and *ex parte* communications, with pedicle screw spinal system manufacturers and had participated substantially in the design of the Cohort study, thereby compromising their impartiality.

FDA disagrees in part. While it is expected that Panel members, who are experts in a given field, will often have some financial interests related to that field (e.g., certain arrangements with a manufacturer (designing a device sold by a particular manufacturer; serving as a consultant to a manufacturer; or receiving funding, directly or indirectly, for research), the required FDA conflict-of-interest questionnaire (FDA From 2725a) enables FDA to identify conflicts-of-interest with a device or manufacturer that all substantial and/or material to the subject of a particular Panel meeting, and thereby facilitates the disclosure and possible waived for the Panel member(s) in order to permit their participation in Panel deliberations.

FDA performed an internal affairs investigation of the Panel members regarding conflicts and ex parte communications . The agency reviewed whether the Panel was properly constituted. Investigation of alleged undisclosed and unwaived conflicts of interest held by Panel members found minor disparities and reporting omissions for two voting Panel members and one nonvoting consultant. The agency has concluded these disparities and omissions were insignificant and did not constitute financial conflicts of interest that would credibly influence their recommendations.

The agency has found that one other voting Panel member had significant undisclosed financial conflicts. However, because the recommendation of the Panel, both in the July 23 meeting and on the subsequent homework assignment, was unanimous and this individual was not controlling, of or unduly influential of, the votes of the other Panel members and was not necessary to constitute a quorum, after expunging the participation of this Panel member, FDA has concluded that this Panel, both in the meeting and on the subsequent homework assignment, was a valid scientific Panel for purposes of making recommendations regarding classification and reclassification.

E. Issues Relating to FDA's Issuance of Regulations

20. One comment argued that, in issuing a classification regulation, FDA may not rely on a scientific study unless it makes publicly available all study data, as well as the identities of the persons who furnished the data. The comment cited 21 CFR 10.20(j), 20.63, and 860.5 as authority. In addition, the comment objected that FDA refused to disclose the identities of the physician-investigators who contributed data to the Cohort study, did not disclose the reformatted IDE analysis, the IDE data, or internal information bearing on the reliability of such data.

FDA disagrees. Although the agency did not disclose the raw IDE or the Cohort study data, or the identities of the clinical investigators who furnished such data to the agency, FDA did provide a detailed analysis of the Cohort Study, the clinical data released by the IDE sponsors, and the meta-analysis (60 FR 51946 at 51960–51962; refs. 51, 65, 66, 119, and 201). FDA believes these publicly available data not only satisfy the requirements under the statute, but provide the public with at least the level of detailed information as that usually available from published reports regularly relied upon to support classification and reclassification.

F. Response to Comments Which Contained Clinical Data

21. Several comments provided clinical information to support the comment's position on the proposed

rule. The submitted clinical information consisted of literature articles describing clinical trials and two questionnaires, a surgeon/patient questionnaire and a lawyer/client questionnaire. The surgeon/patient questionnaire provided mixed results, i.e., some patients were satisfied with their clinical results and others were not satisfied, whereas the lawyer/client questionnaire provided only negative results, i.e., all clients were dissatisfied with their results.

The majority of the articles submitted or referenced in these comments were already reviewed by the Panel and used as part of the basis for their recommendation to classify and reclassify pedicle screw spinal systems into class II. The remainder of these articles were not reviewed by the Panel because they were published after the July 1994, Panel meeting. As described in section V.M of this document, these articles did not raise new issues or concerns relating to the safety or effectiveness of pedicle screw spinal systems. Because of the inherent bias present in the questionnaires, e.g., the total number of questionnaires sent to patients/clients in relation to the number returned and the number included as part of the comment are unknown, the data cannot be used in analyzing the success rate of pedicle screw spinal systems. These data can be used, however, as part of an analysis of the complications. As such, the questionnaires did not describe any complications or raise any issues that had not already been reviewed by the Panel and FDA in making their determinations with respect to the classification and reclassification of pedicle screw spinal systems.

G. Requests for Additional Pedicle Screw Clinical Trials and Data Analyses

22. Ten comments requested that FDA require submission of additional data before finalizing the classification and reclassification of pedicle screw spinal systems. The comments recommended that the following types of data be required: Studies to analyze the long-term effects of the device, continuing evaluations, collections of data using a recommended data report form for obtaining data directly from patients rather than from their surgeons, studies similar to the Cohort study but with larger sample sizes, comprehensive reviews of the literature, and comprehensive reviews of all data. In addition, one comment suggested that FDA was reclassifying these devices without reviewing clinical trial data documenting their safety and effectiveness.

FDA disagrees. As previously explained, under section 513 of the act, devices are classified and reclassified into one of three classes based on *reasonable assurance*, not *absolute proof*, of their safety and effectiveness. The Panel recommended, and FDA concurred, that pedicle screw spinal systems intended to provide immobilization and stabilization of spinal segments in skeletally mature patients as an adjunct to fusion in the treatment of degenerative spondylolisthesis and spinal fractures be classified and reclassified into class II because they determined that premarket approval is not necessary to provide reasonable assurance of safety and effectiveness; general controls alone are insufficient to provide reasonable assurance of the device's safety and effectiveness; and there is sufficient information to establish special controls to provide such assurance. FDA also determined that, when intended to provide immobilization and stabilization of spinal segments in skeletally mature patients as an adjunct to fusion in the treatment of the following acute and chronic instabilities or deformities of the thoracic, lumbar, and sacral spine: Degenerative spondylolisthesis with objective evidence of neurologic impairment, fractures, dislocations, scoliosis, kyphosis, spinal tumors, and failed previous fusion attempts (pseudarthrosis), special controls would provide a reasonable assurance of safety and effectiveness. The Panel and FDA reached these conclusions only after considering a substantial amount of valid scientific evidence. As described previously, this valid scientific evidence consisted of clinical data collected from three sources—data from IDE's (the reformatted IDE data), data from the literature (the meta-analysis), and data collected directly from surgeons (the Cohort study). The IDE data was prospective clinical data collected under the protocols of FDA-approved clinical trials. The meta-analysis was retrospective clinical data published in peer-reviewed literature. The Cohort study consisted of retrospective nationwide clinical data collected from surgeons of various experience levels from a patient population that was homogeneous in terms of diagnosis, but mixed in terms of severity of disease. In addition to these sources of clinical data, MDR and MedWatch reports were analyzed for device problems. FDA does not believe that it is necessary to require submission of additional data, to conduct additional studies, or to re-review the literature before classifying and reclassifying these devices. FDA does agree, however, that the longer-term performance of these devices is not fully characterized. For this reason, postmarket surveillance (PMS) studies will be required.

H. Issues Relating to Indications for Use

Over 200 comments addressed the various intended uses of pedicle screw spinal systems.

23. Twenty-three comments questioned FDA's authority to regulate the indications for use of medical devices. They believed that, although restrictions on the use of pedicle screw spinal systems may be appropriate, this aspect of medical device regulation is outside the scope of FDA's authority and should be decided by professional societies, peer review groups, credentialing organizations, and hospitals. One comment stated that FDA should regulate the safety of medical devices only for certain indications. Several other comments stated that there should be no restrictions on the use of pedicle screw spinal systems. All of these comments argued that FDA's actions interfered with the practice of medicine.

FDA disagrees. In determining whether or not a device is safe and effective, FDA first considers the intended uses for the device. Spinal fusion is not a medical indication but a treatment option which can be approached in a variety of ways. It is one of the desired outcomes from using pedicle screw spinal systems. FDA recognizes, however, that fusion in and of itself is not what patients with spinal disease are seeking. They wish to be relieved of their symptoms, have their objective impairment alleviated, and avoid more symptomatic or functional impairment. Devices that share the same outcome for a given condition do not necessarily share the same benefits and risks. One of the aspects in determining if a device may be legally marketed is deciding, based on the available data, what the appropriate indications are. A device may be an appropriate treatment for one indication, but not for another. In addition, to understand the evidence supporting a device's safety and effectiveness, a distinct medical condition requiring treatment must be identified. In reviewing the valid scientific evidence, the Panel recommended and FDA found that the use of pedicle screw spinal systems were safe and effective only for certain indications. The valid scientific evidence did not support unrestricted use of the device.

In determining the safety and effectiveness of a device for the purpose

of classification or reclassification, both the Panel and the agency are to consider the persons for whose use the device is represented or intended, the conditions of use for the device, and the probable benefit to health from the use of the device weighed against any probable injury or illness from such use (§ 860.7(b)). The device is to be considered, not in a vacuum, but rather in the context of the patient population for whose use it is intended. Accordingly, there is reasonable assurance that a device is safe when it can be determined that the probable benefits to health from use of the device for its intended uses and conditions of use outweigh any probable risks (§ 860.7(d)(1)). The benefits and risks to health presented by a device depend, in large part, on the specific use for which the device is intended. There may be reasonable assurance that a device is safe for some, but not other, uses. Similarly, there is reasonable assurance that a device is effective when it can be determined that, ''in a significant portion of the target population,'' the use of the device for its intended uses and conditions of use will provide clinically significant results (§ 860.7(e)(1) (emphasis added)). It is clear, then, that when making determinations regarding the classification or reclassification of a device, it is appropriate for the agency to consider the specific intended uses of a device, including the specific patient populations for which it is intended. Consequently, the agency disagrees that it does not have authority to regulate the indications for use for pedicle screws and that it is interfering with the practice of medicine.

24. One comment objected that FDA's proposed reclassification improperly exceeded the recommendations of the Panel.

The Panel determined that the evidence demonstrated a reasonable assurance of safety and effectiveness of pedicle screw spinal systems intended for two severe and diagnostically distinct indications—fracture and degenerative spondylolisthesis. Accordingly, the Panel recommended that the device be classified and reclassified into class II only when intended for these uses. FDA proposed that the device also be classified and reclassified into class II when intended for the following acute and chronic mechanical instabilities or deformities of the thoracic, lumbar, and sacral spine: degenerative spondylolisthesis with objective evidence of neurologic impairment, fractures, dislocations, scoliosis, kyphosis, spinal tumors, and failed previous fusion (pseudarthrosis). FDA disagrees that it exceeded its authority. 21 CFR 860.3(h) defines a classification panel as an advisory committee established by the Commissioner for the purpose of making ''recommendations'' (emphasis added) to the Commissioner on the classification/reclassification of devices. These recommendations are designed to assist the Commissioner in the proper classification and/or reclassification of a device. While FDA usually follows a Panel's recommendations, it is not required to do so.

As stated in the preamble to the proposed rule, FDA believes that sufficient clinical data exist to classify and reclassify into class II pedicle screw spinal systems intended for degenerative spondylolisthesis with objective evidence of neurologic impairment, fractures, dislocations, scoliosis, kyphosis, spinal tumors, and failed previous fusion (pseudarthrosis). The medical literature and data from IDE clinical investigations provide adequate evidence that the device can safely and effectively stabilize the spine and maintain spinal alignment while fusion takes place. The risks associated with the use of pedicle screw spinal systems intended to provide immobilization and stabilization of spinal segments as an adjunct to fusion in the treatment of these acute and chronic instabilities or deformities of the thoracic, lumbar, and sacral spine are similar to those associated with other class II spinal implant devices, such as those classified in § 888.3050 (21 CFR 888.3050) (60 FR 51946 at 51956).

25. Several comments advocated classifying and reclassifying into class II pedicle screw spinal systems intended for additional uses, including degenerative disc disease, degenerative deformities, stenosis, iatrogenic instability and previous multiple laminectomies, facet joint disease, pseudospondylolisthesis, low back pain, disc herniation, arthritis, and osteomyelitis.

FDA believes that valid scientific evidence does not currently exist to support classifying and reclassifying into class II pedicle screw spinal systems when intended for the indications listed above. Neither the literature nor the clinical data establish the safe and effective use of pedicle screw spinal systems for degenerative disc disease, degenerative deformities, stenosis, iatrogenic instability and previous multiple laminectomies, facet joint disease, pseudospondylolisthesis, low back pain, disc herniation, arthritis, or osteomyelitis. As stated in the preamble to the proposed rule, FDA has determined that, when intended for use in conditions not categorized as acute or chronic instabilities or deformities of the thoracic, lumbar, and sacral spine, premarket approval is necessary to ensure the safety and effectiveness of the device (60 FR 51946 at 51957). FDA-approved clinical trials for some of these indications are ongoing. When data from these or other studies become available for any of the indications described above, they may be submitted in either an application for premarket approval or reclassification petition.

26. Eight comments advocated adding specific pediatric indications and one comment advocated adding general pediatric use to the list of indications. The specific indications included myelodysplasia, spina bifida, cerebral palsy, muscular dystrophy, myelomeningocele, and congenital subluxation.

FDA disagrees. As stated previously, all valid scientific evidence reviewed by the Panel and FDA were obtained from skeletally mature populations. To date, the safety and effectiveness of pedicle screw spinal systems in pediatric populations have not been demonstrated. Therefore, this patient population is excluded from this classification and reclassification. When intended for use in pediatric populations, pedicle screw spinal systems are considered postamendments class III devices for which premarket approval is required.

27. Several comments addressed ways in which FDA should further limit the indications for use of pedicle screw spinal systems, such as by including specific patient evaluation criteria or by specifying the severity of the condition.

FDA disagrees that these actions are necessary. FDA classifies devices based upon, among other things, patient selection, not individual patient management. FDA notes that it is the responsibility of individual surgeons to determine the appropriateness of using a specific medical device for a given patient.

28. Four comments stated that pedicle screw spinal systems should not be allowed on the market for any use. Another comment requested that an additional Panel meeting be convened to discuss further restricting the intended uses of pedicle screw spinal systems.

FDA disagrees. After reviewing all available data and information, FDA believes that there is reasonable assurance that pedicle screw spinal systems are safe and effective for certain intended uses. FDA does not believe that pedicle screw spinal systems present a substantial deception or an

unreasonable and substantial risk of illness or injury. Consequently, FDA does not believe it would be appropriate to ban them under section 516 of the act (21 U.S.C. 360f).

FDA also disagrees that an additional Panel meeting is necessary because the relevant available data have been reviewed.

I. Issues Relating to Special Controls

29. One comment asserted that PMS studies cannot legally be required for pedicle screw spinal systems because the devices are not intended for use in supporting or sustaining life and pose risks no different from those associated with the use of other preamendments class II spinal fixation devices.

FDA disagrees. Under section 522 of the act (21 U.S.C. 360l), postmarket surveillance is required for certain devices and may be required for any device for which FDA determines that it is necessary to protect the public health or to provide safety or effectiveness data for the device. FDA has determined that PMS studies are necessary to provide longer-term data on the safety and effectiveness of pedicle screw spinal systems.

Although originally proposed as a special control, FDA has determined that PMS studies are best imposed by order in the substantial equivalence determination letter for each device. This will preserve the discretionary nature of the PMS studies and will allow the agency to more easily remove the requirement once it determines that these studies are no longer necessary to assure the safety and effectiveness of pedicle screw spinal systems. The final regulation has been modified to reflect that PMS studies are no longer one of the special controls for these devices.

30. One comment stated that PMS studies are appropriate only for devices cleared for marketing with limited clinical performance data. The comment noted that there now exists a vast amount of clinical information gained from use of pedicle screw spinal systems in several thousand patients. The comment also noted that, based on these data, the Panel concluded that, with respect to safety and effectiveness, these devices are comparable to, or better than, currently available spinal systems. The comment concluded that this clinical information and the conclusions drawn from this information provide sufficient clinical data to adequately identify and characterize the performance of pedicle screw spinal systems and the issues pertinent to safety and effectiveness, thereby obviating the need to conduct PMS studies.

FDA disagrees that PMS studies are appropriate only for devices cleared for marketing with limited clinical performance data. Section 522 of the act allows FDA to require PMS studies for any device for which it determines such studies would protect the public health or provide safety or effectiveness data for the device. As stated in the preamble to the proposed rule, FDA will require PMS studies in order to address issues related to device specific design differences, surgical techniques, and device usage (60 FR 51946 at 51955). Although there is ample short-term clinical performance data for these devices, there does not now exist sufficient longer-term, i.e., more than 24-month followup, safety and/or effectiveness data regarding device specific design differences, surgical techniques, and device usage.

31. A second comment noted that components used to construct pedicle screw spinal systems could be identical to those used to construct either spinal interlaminal fixation orthoses (§ 888.3050) or spinal intervertebral body fixation orthoses (21 CFR 888.3060). Because PMS studies are not required for these devices, they should not be required for pedicle screw spinal systems. A third comment believed that PMS studies are inappropriate for well-established, standard of care treatments involving medical devices that were in existence prior to the 1976 amendments, including pedicle screw spinal systems.

FDA disagrees that PMS studies are inappropriate for devices that were in existence prior to the 1976 amendments. Section 522(a)(2) of the act specifically authorizes FDA to require a manufacturer to conduct PMS studies for any device, regardless of when it was first introduced or delivered for introduction into interstate commerce, for which FDA determines that PMS studies are necessary to protect the public health or to provide safety or effectiveness data for the device. Although, as the comment states, certain devices have been used as pedicle screw spinal systems for some time, except for the limited severe spondylolisthesis intended use available since January 1995, pedicle screw spinal systems have not been legally marketed. Collection of the PMS study data will allow FDA to analyze information on the use of devices specifically intended, and legally marketed, for use as pedicle screw spinal systems.

32. Five comments believed that PMS studies are unnecessary and will not further protect the public health because one or more of the following current reporting systems already provides adequate information on the performance of pedicle screw spinal systems: (1) The MDR System, (2) Voluntary Reporting under MedWatch, (3) User Reporting, and (4) Complaint Handling under the current good manufacturing practices. One comment supported a requirement that labeling remind surgeons they are required to report certain events under MDR. Two comments suggested that a statement which encourages health care professionals to submit MDR's under the Voluntary MedWatch System be placed in the required package insert of the device. Two other comments noted that no other class II spinal implant device is subject to PMS studies. Three comments also stated that collecting additional information will increase health care costs.

FDA disagrees in part. The purposes of PMS studies and current reporting systems are different. PMS studies are active investigations of device performance during actual use, whereas other reporting systems, i.e., MedWatch, MDR, User Reporting, and Complaint Reporting, are passive reporting mechanisms. As such, these current reporting systems would not provide the agency with clinical monitoring information on pedicle screw spinal systems other than unexpected problems in the marketplace. The PMS studies, in contrast, will provide longer-term safety and effectiveness data for pedicle screw spinal systems once the devices are distributed in the general population under actual conditions of use. Finally, FDA is aware that PMS studies might have an impact on health care costs. Although this is unfortunate, the agency believes that it is necessary to impose this requirement and collect this information in order to assure the safety and effectiveness of pedicle screw spinal systems.

33. A comment suggested that, due to the litigious climate surrounding these devices, it may be very difficult for manufacturers to recruit surgeons to participate in PMS studies.

FDA recognizes the concern that there may be conditions which would make the collection of the data somewhat difficult. However, FDA believes that it is important that the data be obtained and that it is possible to recruit a sufficient number of surgeons to participate in PMS studies.

34. One comment stated that the proposed identification for pedicle screw spinal systems was inaccurate, or at least misleading. The comment noted that, as proposed, a pedicle screw spinal system assembly must contain all of the components listed as part of the pedicle screw spinal system. The comment stated that, for any given assembly,

some or all of the system components could be used.

FDA agrees in part. As proposed, the identification could be interpreted to require that all of the described components were necessary to construct a pedicle screw spinal system assembly. FDA has amended the identification of the device to clarify that not all of the described components are required to be used in a pedicle screw spinal system assembly.

35. In the preamble to the proposed rule, FDA proposed two labeling special controls. These controls described the intended uses and indications for pedicle screw spinal systems and cautioned the user about potential risks to health if the devices were used under certain conditions. Three comments stated that the two labeling special controls were incorrectly categorized as ''warnings'' according to FDA's General Program Memorandum No. G91–1, ''Device Labeling Guidance.'' They believed that these labeling requirements are more appropriately described as ''precautions'' or ''important notes'' because they describe a particular patient population and not specific risks or hazards associated with the use of a device. Four comments objected that: (1) Use of the phrase ''* * * with significant potential risk for serious injury to patients * * *'' in the second labeling statement did not accurately reflect the data reviewed by the Panel to make its recommendation,(2) references to training and experience should not be part of the second labeling special control, and (3) the controls containing the language referred to in (1) and (2) should be removed or modified.

FDA agrees with the comments that the two labeling special controls should be rewritten, but disagrees with the specific reasons. General Program Memorandum No. G91–1 states that ''A warning is appropriate when the device is commonly used for a disease or condition for which there is a lack of valid scientific evidence of effectiveness for that disease or condition and such usage is associated with a serious risk to health * * * Include an appropriate warning if there is reasonable evidence of an association of a serious hazard with the use of the device. A causal relationship need not have been proved.'' This is the case when pedicle screw spinal systems are used for indications other than significant mechanical instabilities or deformities of the thoracic, lumbar, and sacral spine. Because valid scientific evidence is not available to support a determination that a reasonable assurance exists that pedicle screw spinal systems are safe and effective for other indications, categorizing the first labeling special control as a ''warning'' is the appropriate mechanism to alert users to the potential for injury to a patient.

The second labeling special control does not warrant being described as a ''warning'' because it does not meet the definition of this term. It does not describe known serious adverse reactions or known potential safety hazards; it does not provide specific steps to be taken; it does not concern a use for which there is reasonable evidence of association with a serious hazard. It does, however, provide information on special care to be exercised by a practitioner, although the need for special care is implied, not explicitly stated. Accordingly, FDA concludes that it is more appropriately categorized as a ''precaution''.

After reviewing the proposed special controls regarding labeling, FDA has concluded that the information should be stated more clearly. FDA believes that the labeling special controls reflect the data reviewed by the Panel. FDA also believes that the labeling special controls are necessary to provide reasonable assurance of the safety and effectiveness of the devices. Finally, as described in the next section, the intent of the second control was not to specify the type of training that should be available or to suggest that FDA would provide or approve any training. Rather, it was intended to alert surgeons to the necessity of receiving appropriate training in the use of specific pedicle screw spinal systems. Because of concerns with the proposed wording, the labeling special controls have been modified to read as follows:

''**Warning**: The safety and effectiveness of pedicle screw spinal systems have been established only for spinal conditions with significant mechanical instability or deformity requiring fusion with instrumentation. These conditions are significant mechanical instability secondary to degenerative spondylolisthesis with objective evidence of neurologic impairment, fracture, dislocation, scoliosis, kyphosis, spinal tumor, and failed previous fusion (pseudarthrosis). The safety and effectiveness of these devices for any other conditions are unknown.''

''**Precaution**: The implantation of pedicle screw spinal systems should be performed only by experienced surgeons with specific training in the use of this pedicle screw spinal system because this is a technically demanding procedure presenting a risk of serious injury to the patient.''

36. A number of comments stated that appropriate surgeon training should be required prior to use of pedicle screw spinal systems and that classification/reclassification into class II would make access to training and device information easier. In addition, several comments believed that professional societies and hospitals, not FDA or the manufacturers, should determine what constitutes adequate training for surgeons implanting pedicle screw spinal systems.

FDA agrees that it is important that surgeons who use pedicle screw spinal systems have proper training prior to using the device. FDA does not believe, however, that it should identify who is most qualified to provide such training or determine what constitutes adequate training. The precaution statement is intended to inform surgeons (and patients) of the possible effect the device could have on the patient if the surgeon implanting the device is not trained or experienced in the proper use of pedicle screw spinal systems. This includes knowledge of the indications, patient selection criteria, and appropriate surgical techniques.

37. A comment questioned the proposed warning label because, in the past, FDA has prohibited pedicle screw spinal system manufacturers from supporting courses that described surgical techniques of ''off label'' uses demonstrating such uses or providing hands-on workshops to learn such uses.

FDA disagrees. Previously, the agency issued several warning letters to pedicle screw spinal system manufacturers for participating in or supporting the training of practitioners in the use of long bone screw, pedicle fixation because, at that time, no long bone screw devices had received FDA clearance for use in the pedicles of the spine. As a result, FDA considered such use ''off label.'' Because the association with these training programs was considered the promotion of an ''off-label'' use, the agency stated that the manufacturers had misbranded and adulterated the long bone screws in accordance with sections 501(f)(1)(B) and 502(o) of the act (21 U.S.C. 351(f)(1)(B) and 352(o)) and promotion of this use was considered a major modification of the intended use, requiring a new premarket notification (510(k)) submission under § 807.81(a)(3)(ii). The regulations and the act are clear that manufacturers must have clearance for the intended use for which their device(s) are promoted, advertised, or held for sale.

With the issuance of this final regulation, the agency now encourages pedicle screw spinal system manufacturers to support training for the class II intended uses. Such training, however, should not be provided before FDA clearance is received. The above referenced warning label will appear

only on devices that have been cleared for pedicle screw spinal fixation.

38. The comment also claimed that the right to free speech guaranteed by the First Amendment to the U.S. Constitution should not be restricted by FDA's suppression of training for ''off label'' use.

FDA disagrees that its limitations on promotional training conducted or sponsored by manufacturers for ''off label'' uses for pedicle screw spinal systems violate the First Amendment. As described above, the act requires that FDA regulate devices based on their intended use. The term ''intended use'' is broadly defined and encompasses the manner in which a company characterizes its product in the marketplace. The intended use of a device refers to the objective intent of the persons legally responsible for its labeling (§ 801.4 (21 CFR 801.4)). ''The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or *oral or written statements by such persons or their representatives*.'' (§ 801.4 (emphasis added)); (see e.g., *Coyne Beahm, Inc. et al.* v. *United States Food and Drug Administration, et al.*, 958 F. Supp. 1060 (M.D.N.C. 1997).) Consequently, oral statements and materials presented at industry-supported training programs may provide evidence of a device's intended use. If these statements or materials promote a use that has not been approved by the agency, the device is misbranded under section 502(f)(1) of the act for failure to bear labeling with adequate directions for all intended uses, and under section 502(o) of the act because premarket notification was not provided as required under section 510(k) of the act. The device is also adulterated under section 501(f) of the act for failure to have FDA approval. Thus, the various means by which manufacturers and their representatives provide information about their products to healthcare professionals and consumers, including statements and materials presented at industry-supported scientific and educational activities, directly bear on whether a device is improperly promoted and, therefore, adulterated or misbranded.

Because the regulation of devices is an area of extensive Federal regulation, the agency may regulate the communications at industry-supported scientific and educational activities without violating the First Amendment. (Cf. *SEC* v. *Wall Street Publishing Institute, Inc.*, 851 F.2d 365 (D.C.Cir. 1988), cert. denied, 109 S.Ct. 1342 (1989).) Moreover, to the extent that such communications constitute protected speech, they are commercial speech and FDA's regulation of such activities does not violate the First Amendment. (See *Bolger* v. *Youngs Drug Products*, 103 S.Ct. 2875 (1983); *S.U.N.Y.* v. *Fox*, 109 S.Ct. 3028 (1989); *Cincinnati* v. *Discovery Network*, 113 S.Ct. 1505 (1993).) Industry-supported scientific educational activities refer to a specific product, are economically motivated, and propose a commercial transaction. These programs are intended to convince the audience to prescribe, purchase, or otherwise use the particular product.

The Supreme Court has afforded commercial speech limited constitutional protection. (See, e.g., *Virginia State Board of Pharmacy* v. *Virginia Citizens Consumer Council, Inc.*, 96 S.Ct. 1817 (1976); *Central Hudson Gas & Electric Corp.* v. *Public Service Commission*, 100 S. Ct. 2343 (1990).) In *Central Hudson*, the Supreme Court established a four-prong test to determine whether limitations on commercial speech are constitutional. The four prongs are: (1) Whether the speech concerns lawful activity and is not misleading, (2) whether the asserted government interest is substantial, (3) whether the limitation directly advances the governmental interest asserted, and (4) whether the limitation is not more extensive than is necessary to serve that interest. The Court has clarified that the fourth prong requires that the restriction be ''narrowly tailored'' to serve the asserted government interest. Narrow tailoring means a fit that is reasonable. (See *S.U.N.Y.* v. *Fox*, 109 S.Ct. 3028. 3035 (1989).)

FDA's regulation of industry-supported scientific and educational activities satisfies all four prongs. First, as previously discussed, industry-supported scientific and educational activities that promote an unapproved device, or promote an approved device for an unapproved use, create an unlawful product—a misbranded or adulterated device. Accordingly, industry-supported activities that promote unlawful products concern illegal activity and may be prohibited. Second, FDA's limitations on promotional activities with respect to off label uses serve the substantial government interest of protecting the public health and safety by helping to ensure the dissemination of truthful and nonmisleading information about devices. The Supreme Court has repeatedly held that the government's ''interest in the health, safety, and welfare of its citizens constitutes a substantial interest.'' (*Posadas de Puerto Rico Associates* v. *Tourism Co.*, 106 S.Ct. 2968, 2977 (1986); *Rubin* v. *Coors*, 115 S.Ct. 1585, 1591 (1995).) The limitations also serve the second substantial government interest of protecting the public health by preserving the integrity of the premarket approval process under which manufacturers are required to establish that their devices are safe and effective for each of their intended uses before they may be marketed and promoted for those uses. Third, FDA's limitations on promotional activities with respect to off-label uses directly advance the government's substantial interests in protecting the public health and safety by helping to ensure the dissemination of truthful and nonmisleading information about devices and by preserving the integrity of the premarket approval process by dissuading manufacturers from using such activities as a means to promote unapproved products and unapproved uses, thereby encouraging scientific research and avoiding unnecessary harm to patients. Finally, FDA's limitations on industry-sponsored training sessions are narrowly tailored and are a reasonable approach to protect the public health and safety by discouraging the dissemination of misleading or biased information, and by maintaining the integrity of the premarket approval process. FDA's limitations apply only to industry-supported activities that relate to the supporting company's device or to competing devices. They are directed to the regulated sponsors of such activities, and do not apply to participating professionals or independent scientists and organizations.

39. Several comments believed that the device should be available for use only by neurosurgeons or orthopaedic surgeons supervised by neurosurgeons.

FDA disagrees. According to section 520(e)(1)(B), FDA may not restrict access to medical devices based on specialty or board certification.

J. Other Issues

40. Several comments objected that publication of the proposed rule in the **Federal Register** was not appropriate because the general public is not aware of the **Federal Register**. The comments noted that another vehicle for disseminating the information would have been more appropriate.

FDA disagrees. The act (sec. 513(d)(1) and 513(e)(1)) requires that a proposed rule be published in the **Federal Register** as the formal mechanism to provide all interested parties an opportunity to submit comments when

an advisory panel recommends an initial classification or change in classification for a medical device. Comments are invited from anyone. FDA recognizes that other mechanisms for distribution of this type of information is also appropriate. One of the alternate mechanisms currently being tested is electronic publication on the World Wide Web.

41. Several comments objected to FDA's consideration of public comments, which may contain only anecdotal information, in determining the appropriate class for these devices.

FDA agrees that comments provided by the public may contain anecdotal information that does not meet the definition of valid scientific evidence. However, FDA considers this information along with the information provided in other comments. These anecdotal comments did not raise any issues or comments that were not already addressed by the information that the Panel reviewed in making its determination that safety and effectiveness of pedicle screw spinal systems could be assured by special controls.

42. Six comments disapproved of the release of the PIN's which identified the surgeons participating in the Cohort study.

FDA regrets any problems that may have been caused by this inadvertent release of information. However, release of this information did not affect the quality, integrity, or value of the data upon which the Panel's recommendation was based.

43. A comment noted that there is no consensus among spine surgeons that pedicle screw fixation has become the standard of care or the gold standard for treatment of spinal instability so as to justify the conclusion that the devices are safe and effective and to justify abandonment of the randomized control trial in making such an assessment.

FDA agrees that there is no consensus among spine surgeons regarding pedicle screw spinal systems. However, a medical device does not need to be viewed as the ''gold standard'' in order for the agency to determine that there is reasonable assurance of its safety and effectiveness. Nor is it a requirement for the classification and reclassification process that all members of a medical specialty agree that a particular device should be used under all conditions. It is recognized that certain devices provide their best outcome when used for specific indications. This is one of the reasons why degenerative disc disease is not included as one of the intended uses in the classification and reclassification of pedicle screw spinal systems. Finally, as described above, randomized clinical trials are only one of the types of valid scientific evidence upon which FDA may rely in support of a classification/reclassification determination. Many IDE studies from which the reformatted IDE data came are still being actively pursued by their sponsors and the patients are being actively followed.

K. Labeling of Bone Screws

44. A comment requested FDA to formally rescind its April 8, 1994, and June 15, 1994, letters to manufacturers of bone screws and devices classified under §§ 888.3030 and 888.3040 (21 CFR 888.3030 and 888.3040), directing them to amend their labeling by including the following: ''Warning: This device is not approved for screw attachment or fixation to the posterior elements (pedicles) of the cervical, thoracic, or lumbar spine.'' According to the comment, this labeling requirement will become unnecessary when pedicle screw spinal systems are classified into class II.

FDA disagrees. In this final rule, FDA is classifying and reclassifying only pedicle screw spinal systems intended for screw attachment or fixation to the pedicles of the thoracic, lumbar, or sacral spine for immobilization and stabilization of spinal segments for the treatment of significant medical instability or deformity requiring fusion with instrumentation. This classification and reclassification in no way affects devices classified as single/multiple component metallic bone fixation appliances and accessories (§ 888.3030) or smooth or threaded metallic bone fixation fasteners (§ 888.3040). Those devices are still not approved for screw attachment or fixation to the posterior elements (pedicles) of the cervical, thoracic, or lumbar spine. Hence, the 1994 amended labeling remains appropriate for these devices.

45. One comment noted that in January 1995, FDA began clearing 510(k)'s intended to treat grades 3 and 4 spondylolisthesis at the L_5–S_1 junction. The comment concluded that, by default, grades 1 and 2 spondylolisthesis, less severe conditions, are considered to be postamendments intended uses resulting in the device being automatically classified into class III. According to this comment, this means that FDA, through required manufacturer labeling, is instructing physicians to wait until grades 1 and 2 spondylolisthesis develop into grades 3 and 4 spondylolisthesis before employing treatments utilizing pedicle screw spinal systems, which is not in the patient's best interests.

FDA disagrees. FDA is not limiting physicians, through required manufacturer labeling, to wait until grades 1 or 2 spondylolisthesis develop into grades 3 or 4 spondylolisthesis. FDA is stating that the preamendments documentation in the 510(k) described marketing of the device only for the treatment of grades 3 and 4 spondylolisthesis at L_5–S_1. Treatment of grades 1 or 2 spondylolisthesis does not have to wait until it progresses to grades 3 or 4. Legally marketed devices which do not utilize pedicle screws are available for this purpose.

L. Review of New Pedicle Screw Spinal System 510(k)'s

46. A comment pointed out that since FDA's January 1995, determination regarding the preamendments status of pedicle screw spinal systems in the treatment of severe spondylolisthesis, many 510(k) submissions have been cleared for this use. FDA's proposed rule for pedicle screw spinal systems, once final, will essentially represent a labeling change for these devices, requiring new 501(k) submissions. The comment suggested that the new 510(k)'s should provide a draft copy of the revised labeling and a statement that the previously-cleared device has not been modified in any way that may affect its safety or effectiveness. According to the comment, this limited type of review would facilitate and expedite the review process and would not unnecessarily burden FDA's device evaluation staff.

FDA agrees with this approach and intends to apply it in its review of 510(k)'s for pedicle screw spinal systems that were cleared previously for use in severe spondylolisthesis. Pedicle screw spinal systems which have not been previously reviewed, or that represent significant modifications compared to the previously cleared device(s), will require a complete 510(k) submission, including the device labeling.

M. Review of New Information Published and Submitted After Publication of the Proposed Rule: Pedicle Screw and Related Literature and MedWatch and MDR System Reports

FDA performed a comprehensive search of the English-language medical literature published between 1994 and the present. Thirty-five articles pertained to the clinical performance of pedicle screw spinal systems. The clinical performance results, e.g., fusion rate and complication types and rates,

from these peer-reviewed articles did not differ from those previously reported in the preamble to the proposed rule for either pedicle screw spinal systems or the group of class II spinal devices using hooks and/or wires or noninstrumented fusions.

FDA also performed a review of the MedWatch and MDR databases from 1994 to the present. The complications associated with pedicle screw spinal systems during this period were comparable to those reported in the preamble to the proposed rule for pedicle screw spinal systems and the group of class II spinal devices using hooks and/or wires and noninstrumented fusions.

VI. References

The following references have been placed on display in the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. These references may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Rodgers, A. E., ''FDA Pedicle Screw Cohort Study: Audit Findings,'' July 30, 1996.

2. Richter, K. C., ''Assessment of the Impact of BIMO Audit Findings for the Pedicle Screw Cohort Study on Study Results,'' August 29, 1997.

VII. Environmental Impact

The agency has determined under 21 CFR 25.24(e)(2) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Analysis of Impacts

FDA has examined the impact of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612) (as amended by Subtitle D of the Small Business Regulatory Fairness Enforcement Act of 1996 (Pub. L. 104–121), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4)). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule has been determined to be a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Classification and reclassification of the device from class III to class II when the device is intended to provide immobilization and stabilization of spinal segments as an adjunct to fusion in the treatment of the following acute and chronic instabilities or deformities of the thoracic, lumbar, and sacral spine: Degenerative spondylolisthesis with objective evidence of neurologic impairment, fractures, dislocations, scoliosis, kyphosis, spinal tumors, and failed previous fusion attempts (pseudarthrosis) will relieve all manufacturers of the device of the cost of complying with the premarket approval requirements in section 515(b) of the act.

Because classification and reclassification will reduce regulatory costs with respect to this device, it will not impose significant economic impact on any small entities, and it may permit small potential competitors to enter the marketplace by lowering their costs. The Commissioner of Food and Drugs, therefore, certifies that this final rule will not have a significant economic impact on a substantial number of small entities. In addition, this final rule will not impose costs of $100 million or more on either the private sector or State, local, and tribal governments in any one year, therefore, a summary statement of analysis under section 202(a) of the Unfunded Mandates Reform Act of 1995 is not required.

List of Subjects in 21 CFR Part 888

Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 888 is amended as follows:

PART 888—ORTHOPEDIC DEVICES

1. The authority citation for 21 CFR part 888 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

2. Section 888.3070 is added to subpart D to read as follows:

§ 888.3070 Pedicle screw spinal system.

(a) *Pedicle screw spinal systems*—(1) *Identification*. Pedicle screw spinal systems are multiple component devices, made from a variety of materials, including alloys such as 316L stainless steel, 316LVM stainless steel, 22Cr–13Ni–5Mn stainless steel, Ti–6Al–4V, and unalloyed titanium, that allows the surgeon to build an implant system to fit the patient's anatomical and physiological requirements. Such a spinal implant assembly consists of a combination of anchors (e.g., bolts, hooks, and/or screws); interconnection mechanisms incorporating nuts, screws, sleeves, or bolts; longitudinal members (e.g., plates, rods, and/or plate/rod combinations); and/or transverse connectors. The devices are intended to provide immobilization and stabilization of spinal segments in skeletally mature patients as an adjunct to fusion in the treatment of the following acute and chronic instabilities or deformities of the thoracic, lumbar, and sacral spine: degenerative spondylolisthesis with objective evidence of neurologic impairment, fracture, dislocation, scoliosis, kyphosis, spinal tumor, and failed previous fusion (pseudarthrosis).

(2) *Classification*. Class II (special controls). Pedicle screw spinal systems must comply with the following special controls:

(i) Compliance with material standards,

(ii) Compliance with mechanical testing standards,

(iii) Compliance with biocompatibility standards, and

(iv) Labeling which contains these two statements in addition to other appropriate labeling information:

''**Warning**: The safety and effectiveness of pedicle screw spinal systems have been established only for spinal conditions with significant mechanical instability or deformity requiring fusion with instrumentation. These conditions are significant mechanical instability or deformity of the thoracic, lumbar, and sacral spine secondary to degenerative spondylolisthesis with objective evidence of neurologic impairment, fracture, dislocation, scoliosis, kyphosis, spinal tumor, and failed previous fusion (pseudarthrosis). The safety and effectiveness of these devices for any other conditions are unknown.''

''**Precaution**: The implantation of pedicle screw spinal systems should be performed only by experienced spinal surgeons with specific training in the use of this pedicle screw spinal system because this is a technically demanding procedure presenting a risk of serious injury to the patient.''

(b) *Pedicle screw spinal systems for all other uses*—(1) *Identification*. Pedicle screw spinal systems for all other uses are multiple component devices, made from a variety of materials, including alloys such as 316L stainless steel, 316LVM stainless steel, 22Cr–13Ni–5Mn stainless steel, Ti–6Al–4V, and unalloyed titanium, that allow

the surgeon to build an implant system to fit the patient's anatomical and physiological requirements. Such an spinal implant assembly consists of a combination of anchors (e.g., bolts, hooks, and/or screws); interconnection mechanisms incorporating nuts, screws, sleeves, or bolts; longitudinal members (e.g., plates, rods, and/or plate/rod combinations); and/or transverse connectors.

(2) *Classification*. Class III (premarket approval).

(c) *Date PMA or notice of completion of a PDP is required*. An approved PMA or a declared completed PDP must be in effect before placing the device in commercial distribution. See § 888.3.

Dated: April 22, 1998,

Michael A. Friedman,

Lead Deputy Commissioner for the Food and Drug Administration.

Donna E. Shalala,

Secretary of Health and Human Services.

[FR Doc. 98–19944 Filed 7–23–98; 8:45 am]

BILLING CODE 4160–01–F

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 52

[IN75; FRL–6129–7]

Approval and Promulgation of Implementation Plan; Indiana

AGENCY: Environmental Protection Agency.

ACTION: Final rule.

SUMMARY: The United States Environmental Protection Agency (USEPA) is approving Indiana's request to grant an exemption for the northwest Indiana (Lake and Porter Counties) severe ozone nonattainment area from the applicable Oxides of Nitrogen (NO_X) transportation conformity requirements. The USEPA proposed approval on January 6, 1998. The proposal was based on information the Indiana Department of Environmental Management (IDEM) submitted to the USEPA as a State Implementation Plan (SIP) revision request for an exemption under section 182(b)(1) of the Clean Air Act (Act). The technical basis for IDEM's request was the urban airshed modeling (UAM) conducted for an attainment demonstration for the Lake Michigan Ozone Study (LMOS) modeling domain.

DATES: This rule is effective August 26, 1998.

ADDRESSES: Copies of the SIP revision, public comments and USEPA's responses are available for inspection at the following address: United States Environmental Protection Agency, Region 5, 77 West Jackson Boulevard, Chicago, Illinois 60604. (It is recommended that you telephone Patricia Morris at (312) 353–8656 before visiting the Region 5 Office.)

FOR FURTHER INFORMATION CONTACT: Patricia A. Morris, Regulation Development Section (AR–18J), Air Programs Branch, Air and Radiation Division, United States Environmental Protection Agency, Region 5, 77 West Jackson Boulevard, Chicago, Illinois 60604, Telephone Number (312) 353–8656.

SUPPLEMENTARY INFORMATION:

I. Background

Clean Air Act section 176(c)(3)(A)(iii) requires, in order to demonstrate conformity with the applicable SIP, that transportation plans and Transportation Improvement Programs (TIPs) contribute to emissions reductions in ozone and carbon monoxide nonattainment areas during the period before control strategy SIPs are approved by USEPA. This requirement is implemented in 40 CFR 93.119, which establishes what is known as the ''build/no-build test.'' The conformity requirements of 176(c)(3)(A) are more fully explained in the notice of proposed rulemaking (63 FR 456, January 6, 1998).

On July 13, 1994, the States of Illinois, Indiana, Michigan, and Wisconsin (the States) submitted to the USEPA a petition for an exemption from the requirements of section 182(f) of the Clean Air Act (Act). The States, acting through the Lake Michigan Air Directors Consortium (LADCo), petitioned for an exemption from the Reasonably Available Control Technology (RACT) and New Source Review (NSR) requirements for major stationary sources of NO_X. The petition also asked for an exemption from the transportation and general conformity requirements for NO_X in all ozone nonattainment areas in the Lake Michigan Modeling domain.

On March 6, 1995, the USEPA published a rulemaking proposing approval of the NO_X exemption petition for the RACT, NSR and transportation and general conformity requirements. A number of comments were received on the proposal. Several commenters argued that NO_X exemptions are provided for in two separate parts of the Act, in sections 182(b)(1) and 182(f), but that the Act's transportation conformity provisions in section 176(c)(3) explicitly reference section 182(b)(1). In April 1995, the USEPA entered into an agreement to change the procedural mechanism through which a NO_X exemption from transportation conformity would be granted (*EDF et al.* v. *USEPA*, No. 94–1044, U.S. Court of Appeals, D.C. Circuit). Instead of a petition under 182(f), transportation conformity NO_X exemptions for ozone nonattainment areas that are subject to section 182(b)(1) now need to be submitted as a SIP revision request. The northwest Indiana ozone nonattainment area is classified as severe and, thus, is subject to section 182(b)(1). Thus, the NO_X waiver for transportation conformity would have been granted in January 26, 1996, at the same time as the waiver for RACT, NSR and general conformity except for the technical correction to require a SIP revision request under 182(b)(1).

The transportation conformity requirements are found at sections 176(c)(2), (3), and (4) of the Act. The conformity requirements apply on an areawide basis in all nonattainment and maintenance areas. The USEPA's transportation conformity rule was amended on August 29, 1995 (60 FR 44762) to reference section 182(b)(1) rather than 182(f) as the means for exempting areas subject to section 182(b)(1) from the transportation conformity NO_X requirements.

The May 24, 1996, SIP revision request from Indiana was submitted to meet the requirements in accordance with 182(b)(1). Public hearings on this SIP revision request were held on June 11, 1996.

In evaluating the 182(b) SIP revision request, the USEPA considered whether additional NO_X reductions would contribute to attainment of the standard in the northwest Indiana severe ozone nonattainment area and also in the downwind areas of the LMOS modeling domain. The USEPA granted a NO_X waiver for RACT, NSR, and general conformity based on the submitted modeling on January 26, 1996, (61 FR 2428). At the same time and using the same technical support evaluation, the USEPA would have granted the transportation conformity waiver but for the technical correction to grant the waiver under 182(b)(1) instead of 182(f). This rulemaking completes the efforts under this technical correction.

On January 6, 1998, (63 FR 456), the USEPA proposed approval of Indiana's request to grant an exemption for the northwest Indiana severe ozone nonattainment area from the applicable NO_X transportation conformity requirements.

II. Public Comments

The USEPA received two sets of comments during the public comment