SUMMARY OF SAFETY AND EFFECTIVENESS

1.0 General Information

DEVICE GENERIC NAME:	Intervertebral Body Fusion Device with Posterior Pedicle Screw Fixation
DEVICE TRADE NAME:	Lumbar I/F Cage® with VSP® Spine System
APPLICANT'S NAME:	DePuy AcroMed, Inc. 3303 Carnegie Avenue Cleveland, Ohio 44115 Telephone: 216-431-9900 Telefax: 216-432-6999
PREMARKET APPROVAL (PMA) APPLICATION NUMBER:	P960025
DATE OF PANEL RECOMMENDATION:	December 11, 1997
DATE OF NOTICE OF APPROVAL TO THE APPLICANT:	February 2, 1999

2.0 Indications for Use

The Lumbar I/F Cage with VSP Spine System is indicated for an open posterior approach using autogenous bone graft in patients with degenerative disc disease (DDD) at one or two spinal levels from L2-S1 whose condition requires the use of interbody fusion combined with posterolateral fusion (360° fusion) and posterior pedicle screw fixation. These patients may have had a previous non-fusion spinal surgery at the involved spinal level(s).

Degenerative disc disease is defined as discogenic back pain with degeneration of the disc confirmed by history and radiographic studies.

3.0 Device Description

The Lumbar I/F Cage with VSP Spine System is composed of two components. The Lumbar I/F Cage component is a spinal interbody fusion device. The VSP Spine System component is a posterior pedicle screw fixation spinal system.

The Lumbar I/F Cage component is made of polymer/carbon fiber composite material. It resembles a parallel-sided box with open faces and closed ends. The inferior and superior surfaces have ridges or teeth that are intended to resist expulsion. The implant has a hollow center to accept packing of autologous bone graft. The posterior end of the implant has a threaded hole for attaching insertion instruments, while the other end is solid with chamfered edges. The I/F Cage is radiolucent. The I/F Cage is provided non-sterile and sterile.

The polymer is poly(ether ketone ether ketone ketone) (PEKEKK, also known as Ultrapek™) and the fibers are polyacrylonitrile (PAN) carbon fibers. The polymer/fiber ratio is 70%/30%. The carbon fibers are 6.35mm long. The carbon fibers and polymer are injection molded into blocks of near net shape and machined into the final form and dimensions of the I/F Cage. To aid in the injection molding process, the carbon fibers are sized with polysulfone. Two small tantalum beads are inserted into the I/F Cage to serve as radiographic markers.

The version of the Lumbar I/F Cage component evaluated in the US clinical trial differed from the device approved in this PMA in several ways. While the polymer and carbon fiber components were chemically identical, they were combined in a different ratio – 70% fiber/30% polymer in the clinical trial compared to 30% fiber/70% polymer in the device to be marketed. In the device evaluated clinically, the carbon fibers were continuous and they were integrated into the polymer through a compression molding process. Finally, this device did not utilize the polysulfone sizing of the marketed device.

The Lumbar I/F Cage component is available in a variety of sizes. The 25mm length I/F Cage is available in 9 sizes (width x height): 9mm x 9mm, 9mm x 11mm, 9mm x 13mm, 11mm x 11mm, 11mm x 13mm, 13mm x 13mm, 13mm x 15mm, 15mm x 15mm, and 15mm x 17mm. The 23mm length I/F Cage is available in 2 sizes: 11mm x 11mm and 11mm x 13mm. The 21mm length I/F Cage is available in 2 sizes: 9mm x 9mm and 9mm x 11mm. The device sizes evaluated in the clinical trial are the same as those described in the PMA.

The Lumbar I/F Cage components are implanted using a defined set of instruments. Lumbar I/F Cage instruments are manufactured from stainless steel that conforms to American Society for Standards and Testing (ASTM) F899-94. The size specific instruments, which correspond to the size of the Cage, include the following: PLIF Cage Trials, I/F Cage Impactor Washers, PLIF Broach System with Modular T-Handle, PLIF Wedged Cage Trials, PLIG System with Modular T-Handle, Inter-Body Disc Spreader Blocks, and Disc Shavers. Universal instruments that are used regardless of the size of the I/F Cage include: I/F Cage Inserter, Cannula Shaft Lock Spreader Insertion Tool, Threaded Shaft Spreader Inserter, Double Ended Impactors (round and square end). All I/F Cage instruments are provided non-sterile and must be sterilized before use or reuse.

The VSP Spine System component consists of several components. As described above for the Lumbar I/F Cage component, the type and sizes of VSP Spine System components used in the clinical trial were the same as those proposed in the PMA.

Stainless Steel AcroMed Pedicle Screws are fabricated from ASTM F-1314 implant grade stainless steel. Stainless Steel AcroMed Pedicle Screws are rigidly fixed to VSP Spine Plates utilizing a double nut locking system. The Stainless Steel AcroMed Pedicle Screw is available in the following diameters: 5.5mm, 6.25mm, 7.0mm, 7.75mm, and available in cancellous thread lengths in 5 mm increments.

VSP Spine Plates are fabricated from ASTM F-138 implant grade stainless steel. VSP Spine Plates have nested slots and variable lengths (41 to 159mm). The plates have between one and four slots and increase in length by half slot increments.

VSP Spine Washers have a chamfered inner hole for proper fit over the integral nut. Washers are manufactured from implant grade ASTM F-138 or F-1314 stainless steel. A wedge shaped washer is available to fill non-symmetric gaps. VSP Spine Washers are available in 3mm and 5mm heights.

The VSP Transverse Connector provides a cross-link connection between parallel VSP Spine Plates. The VSP Connector is manufactured from implant grade ASTM F-138 stainless steel. The connector construct consists of two components: a smooth 3/16" diameter rod, and a pair (one left and one right) of connectors.

The VSP Spine System components are implanted using a defined set of instruments. VSP Spine System instruments are manufactured from stainless steel that conforms to ASTM F899-94, unless otherwise specified. VSP instruments include: Small Iliac Probe, Bone Probe, Modular Taps, Screw Wrench, Nut Wrench, Screw Gauge, Screw Alignment Rods (aluminum), Side Handle Wrenches, Foraminal Probe Set, Quick-Release T-Handle, Sounding Probe, Contouring Template Set (aluminum), Cannulated Screw Cutter, Sacral Depth Sounder, Open-end Wrench and Bone Plate Manipulator.

4.0 Contraindications

The Lumbar I/F Cage with VSP Spine System should not be implanted in patients with active systemic infection or infection localized to the site of implantation.

5.0 Warnings

When more than two involved spinal levels are treated, longer operative times and higher blood loss are likely to occur.

As the number of previous surgeries at the involved spinal level(s) increases, the potential for intra-operative dural tears increases.

Do not use the Lumbar I/F Cage with VSP Spine System with any other device components. There are no data to support the use of the Lumbar I/F Cage with any other pedicle screw fixation device system other than the VSP Spine System.

6.0 Precautions

Forty patients (40/92 = 43%) required a subsequent intervention (surgical or otherwise) prior to their 24 month follow-up evaluation.

The probability of a patient having a successful outcome and not needing a subsequent intervention (surgical or otherwise) was 43% (95% confidence interval = 33, 53).

Use of the Lumbar I/F Cage with VSP Spine System should only be undertaken after the surgeon has become thoroughly knowledgeable about spinal anatomy and biomechanics; has had experience with PLIF procedures and pedicle screw spinal system fixation; and has had hands-on training in the use of this device.

Two Lumbar I/F Cages should be implanted at each surgical level. Safety and effectiveness have not been established for the use of a single Lumbar I/F Cage component in conjunction with the VSP Spine System components.

Safety and effectiveness have not been established for the use of the Lumbar I/F Cage component without the use of the VSP Spine System component.

The Lumbar I/F Cage with VSP Spine System should not be implanted in patients with severe osteoporosis or osteopenia.

Safety and effectiveness have not been established in patients who did not receive an interbody fusion in conjunction with a posterolateral fusion (360° fusion).

Safety and effectiveness have not been established in patients with the following conditions: three or more levels to be fused; morbid obesity; or pregnancy.

The VSP Spine System components are supplied clean and non-sterile and must be sterilized before use according to the complete sterilization instructions below.

The Lumbar I/F Cage component may be supplied either sterile or non-sterile. When provided non-sterile, it must be sterilized before use according to the complete sterilization instructions below. When supplied sterile, it should be handled with appropriate precautions to maintain sterility.

Implant components can break when subjected to the increased loading associated with delayed union or nonunion.

7.0 Adverse Events

The following complications were reported during a multi-center clinical study of 221 patients treated with the Lumbar I/F Cage with VSP Spine System for the approved indication listed above, as well as other indications.

Complication (%)	Operative (n=221)	1 Month (n=219)	3 Months (n=215)	6 Months (n=210)	12 Months (n=210)	24 Months (n=186)	48 Months (n=92)	Overall (n=221)
Arrhythmia	0.5 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.5 (1)
Broken Cage	0.5 (1)	0.5 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.9 (2)
Broken Pedicle	1.8 (4)	0.0 (0)	0.5 (1)	0.0 (0)	0.0 (0)	0.5 (1)	0.0 (0)	2.3 (5)
Broken screw	0.0 (0)	0.0 (0)	0.0 (0)	1.4 (3)	1.9 (4)	3.8 (7)	1.0	6.3 (14)
Cage displacement	0.5 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.5 (1)
Cardiac[α]	0.0 (0)	1.4 (3)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	1.4 (3)
Death	0.0 (0)	0.9[β] (2)	0.5 (1)	0.0 (0)	0.9 (2)	0.9 (2)	0.0 (0)	3.2 (7)
DIC	0.5 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.5 (1)
Dural tears								
•"incidental" tears[δ]	16.3 (36)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.5[ε] (1)	0.0 (0)	16.7 (37)
•tears requiring post-operative treatment	0.9 (2)	1.8 (4)	0.5 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	3.2 (7)
DVT	0.0 (0)	0.5 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.5 (1)
Embolus	0.0 (0)	0.9 (2)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.9 (2)
Foot drop	0.0 (0)	0.9 (2)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.9 (2)
Ileus	0.0 (0)	0.5 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.5 (1)
Loose screw(s)	0.0 (0)	0.0 (0)	0.0 (0)	0.5 (1)	0.9 (2)	2.2 (4)	0.0 (0)	2.7 (6)
Migrating screw(s)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.9 (2)	0.0 (0)	0.0 (0)	0.9 (2)
Nerve damage	0.5 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.5 (1)
Pneumonia	0.0 (0)	0.0 (0)	0.0 (0)	0.5 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.5 (1)
Psychosocial	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.5 (1)	0.5 (1)	0.0 (0)	0.9 (2)
RSD	0.0 (0)	0.5 (1)	0.5 (1)	0.0 (0)	0.5 (1)	0.0 (0)	0.0 (0)	1.4 (3)
Seroma	0.0 (0)	1.4 (3)	0.9 (2)	0.5 (1)	0.0 (0)	0.5 (1)	0.0 (0)	3.2 (7)
Urinary frequency	0.0 (0)	0.0 (0)	0.5 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.5 (1)
UTI	0.0 (0)	2.7 (6)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	2.7 (6)
Wound infection	0.5 (1)	4.1 (9)	0.9 (2)	0.0 (0)	0.5 (1)	1.1 (2)	0.0 (0)	6.3 (14)

[α]"Cardiac" includes a patient with atrial fibrillation and flutter, a patient who had myocardial infarction that required coronary bypass surgery and a patient with post-operative hypertension. All patients recovered during the post-operative period.

[β]One of these deaths occurred immediately post-operatively as a result of an intra-operative vascular injury with concomitant large blood loss.

[δ]This category describes dural tears which occurred during the index surgery, were repaired during that procedure and had no clinical sequelae.

[ε]This patient experienced a dural tear during surgery to remove the VSP Spine System components at 24 months.

A revision is a procedure which adjusts or in any way modifies the original implant configuration, *e.g.*, adjusting the position of the original configuration, removal of components with their subsequent replacement. A removal is a procedure which removes one or more components of the original implant configuration without replacement of any components. A

reoperation is a procedure which involves any surgical procedure at the involved spinal level(s) which does not remove, modify or add any components. The following table describes the time course distribution of revisions, removals and reoperations for the entire population:

Intervention	Operative n=221	1 Mo. n=215	3 Mo. n=211	6 Mo. n=201	12 Mo. n=181	24 Mo. n=109	36 Mo. n=29	Overall n=221
Revision	0.0	0.0	0.0	0.5	0.9	3.2	1.0	4.1
Removal of VSP	0.0	0.0	0.0	1.4	8.0	28.0	10.1	35.7
Reoperation	0.0	4.6	0.9	0.5	0.9	2.7	0.0	8.1

There were a total of 123 subsequent interventions in the 221 patients that received the Lumbar I/F Cage with VSP Spine System. 60 patients treated for DDD had some form of subsequent intervention. These interventions included, but were not limited to, removal of broken drains, removal of VSP Spine System components, treatment of infections, augmentation of bone graft and epidural/nerve root injections. They are described in the table below.

Subsequent interventions[β]	Number of incidences (%) (n)	
	DDD (n=111)	Total Indications (n=221)
Aspiration of fluid	0.0 (0)	0.5 (1)
Bursitis/seromas over hardware	0.9 (1)	0.5 (1)
Coronary bypass surgery	0.0 (0)	0.5 (1)
Debridement deep infection	2.7 (3)	3.2 (7)
Donor site deep infection	0.9 (1)	0.5 (1)
Excision of lipomas overlying spine	0.9 (1)	0.5 (1)
Morphine pump implantation	0.0 (0)	0.5 (1)
Nerve root sleeve or steroid injection, sympathetic/caudal block	2.7 (3)	2.7 (6)
New pathology	1.8 (2)	2.7 (6)
Removal of broken drain	1.8 (2)	1.4 (3)
Repair of dural tear	3.6 (4)	2.7 (6)
Removal of broken hardware[π]	2.7 (3)	2.7 (6)
Removal of hardware	17.3 (19)	16.3 (36)
Removal of hardware after trauma	0.0 (0)	0.5 (1)
Removal of loose hardware	2.7 (3)	1.8 (4)
Removal of painful hardware	14.5 (16)	14.9 (33)
Replacing hardware with new hardware	1.8 (2)	4.1 (9)

[α]One patient required a coronary bypass operation that was not related to implantation of the Lumbar I/F Cage with VSP Spine System.
[β]Some patients experienced more than one intervention.
[π]The word "hardware" refers to the VSP Spine System components.

The following table contains the averages and ranges (in parentheses) of blood loss and operative time for the Lumbar I/F Cage with VSP Spine System. Values for the Lumbar I/F Cage with

VSP Spine System are reported as those for the total population studied and those for the approved indication of DDD. As noted by the upper end of the ranges from the IDE population, some patients had large amounts of blood. Because a definition for a "normal" amount of blood loss is not available, ranges from the literature are provided for comparison.

	IDE population (average (range))		literature range	
	DDD (n = 110)	all indications (n = 2210)	instrumented	uninstrumented
Blood loss (ml)	1489 (100 – 8200)	1463 (100 – 18,000)	355 - 2760	421 – 1155
Operative time (minutes)	287.5 (175 - 520)	288.5 (120 - 607)	155 - 342	127 - 305

N.B. Although the average values listed above for the DDD patients were often similar to or higher than those for the population as a whole, it should be noted that the width and upper ends of the ranges for the DDD patients were smaller.

Seven patients from the total population who received the Lumbar I/F Cage with VSP Spine System died during the course of the clinical trial. One of the deaths occurred immediately post-operatively. Two of the deaths occurred peri-operatively. None of the deaths were device-related.

The following potential adverse events (singly or in combination) which might be expected to occur, but were not observed in the clinical trial, could also result from the implantation of the Lumbar I/F Cage with VSP Spine System:

1. Bursitis.
2. Decrease in bone density due to stress shielding.
3. Degenerative changes or instability of segments adjacent to fused vertebral levels
4. Fracture of bony structures.
5. Implant material sensitivity, or allergic reaction to a foreign body.
6. Infection, early or late.
7. Nerve damage due to surgical trauma or presence of the device. Neurological difficulties including bowel and/or bladder dysfunction, impotence, retrograde ejaculation, radicular pain, tethering of nerves in scar tissue, muscle weakness, and paraesthesia.
8. Nonunion, delayed union.
9. Discomfort, or abnormal sensations due to the presence of the device.
10. Paralysis.
11. Spinal cord impingement or damage.

12. Vascular damage could result in catastrophic or fatal bleeding. Malpositioned implants adjacent to large arteries or veins could erode these vessels and cause catastrophic bleeding in the late post-operative period.

8.0 Alternative Practices and Procedures

Non-surgical alternatives to performing interbody fusion with the Lumbar I/F Cage with VSP Spine System include, but are not limited to, watchful waiting with no intervention, physical therapy, medications, external bracing, chiropractic care, and exercising. Surgical alternatives include performing posterior lumbar interbody fusion with tricortical iliac crest or bone chip autograft with or without instrumentation, performing interbody fusion with cadaver donor bone allograft with or without instrumentation, and performing an anterior interbody fusion with the same options of autograft or allograft selection, and with or without instrumentation.

9.0 Marketing History

The Lumbar I/F Cage with VSP Spine System has not been marketed for the combined use described in the PMA in any other country.

10.0 Summary of Pre-clinical Testing

10.1 Summary of Mechanical Testing

Several types of mechanical tests were performed on the various components of the Lumbar I/F Cage with VSP Spine System. They can be divided into the following categories:

1. tests to evaluate the version of the Lumbar I/F Cage component used in the clinical trials;
2. tests to evaluate the mechanical equivalence of the IF/Cage component used in the clinical trial compared to the I/F Cage component in the PMA;
3. tests to evaluate the VSP Spine System component containing the 4th generation Stainless Steel AcroMed Pedicle Screws; and
4. tests to evaluate the mechanical equivalence of the 4th generation screw used in the clinical trial to the 5th generation screw contained in the PMA.

In addition to the general categories of tests described above, additional test data were provided. These reports included determinations of the mechanical properties of allograft bone, determinations of the "worst case" construct (*e.g.*, I/F Cage size, Stainless Steel AcroMed Pedicle Screw diameter, etc.), determinations of the impact of marker beads in the I/F Cages, etc. The results of these tests were used, for example, to produce

comparative values for other tests or to determine the impact of intermediate manufacturing steps on the behavior of the final device component configuration. As such, they do not describe the behavior of the device which is the subject of the PMA. While these preliminary data were presented as part of the PMA, they are not reported below. The data contained below only describe the behavior of the final device configurations used in the clinical trial and in the PMA. All values reported below are mean ± standard deviation, unless noted otherwise.

10.1.1 Lumbar I/F Cage component testing summary

Expulsion testing

The Lumbar I/F Cage components were compared to allograft bone for their ability to resist *in vivo* shear loads (pull-out or expulsion testing) after being placed into the disc spaces of human cadaver spines. Either allograft bone or an I/F Cage was placed into the prepared disc space of a specimen. A compressive preload was applied to the specimen. A load perpendicular to this load was then applied directly to the bone or I/F Cage. The load necessary to dislodge the bone or I/F Cage was recorded. Allograft bone required 126.1 ± 83.8N to initiate motion, while a higher load, 352.7 ± 193.4N, was required to move the I/F Cages.

Static and fatigue testing

Initially, data on the version of the I/F Cage used in the clinical trial were provided. Data were then submitted which compared the behavior of this version of the component to that of the version of the I/F Cage component in the PMA. The same test conditions were used in each case. Of the various I/F Cage component sizes available, the size determined through testing to be worst case was finally evaluated.

For each test, the I/F Cage was placed between test blocks which were designed to apply either a compression, compression-shear or torsion load to the component. Loads and displacements were recorded. For the dynamic tests, the load cycle number was also recorded. The static tests involved a single load cycle applied until the component failed, while the dynamic tests involved multiple applications of lower level loads.

Load type	Property	I/F Cage in clinical trial	I/F Cage in PMA
static compression	ultimate load (kN)	6.33 ± 0.51	8.76 ± 0.18
	stiffness (kN/mm)	7.93 ± 0.74	7.88 ± 0.30
static compression shear	ultimate load (kN)	2.83 ± 0.18	6.69 ± 0.56
	stiffness (kN/mm)	8.01 ± 0.43	5.38 ± 0.36
static torsion	ultimate torque (Nm)	8.85 ± 1.01	8.07 ± 0.43
dynamic compression shear	stiffness (Nm/°)	2.50 ± 0.49	1.94 ± 0.15
	asymptotic load level	1400 @ 5 x 10^6 cycles	3400 @ 5 x 10^6 cycles

Because of the presence of polysulfone as a sizing agent in the version of the I/F Cage in the PMA, there was some concern over the impact of environment, particularly lipids, on the device's fatigue behavior. This was evaluated by subjecting both versions of the I/F

Cage to dynamic compression shear loads under various environmental conditions. Except for the change in environment, these tests were conducted in the same manner as the other dynamic tests.

Environment	I/F Cage in clinical trial	I/F Cage in PMA
soybean oil @ 37°C	1900N @ 1.2 x 10^6 cycles$^{\alpha}$	2600N @ 5 x 10^6 cycles
distilled water @ 37°C	1900N @ 2.5 x 10^6 cycles$^{\alpha}$	2600N @ 5 x 10^6 cycles
distilled water @ RT	----	3200N @ <0.5 x 10^6 cycles
air @ RT	----	2900N @ 5 x 10^6 cycles

$^{\alpha}$It was not necessary to cycle these specimens to 5 x 10^6 cycles because this version of the device would not be effected by the lipid environment. In addition, its fatigue behavior had already been determined to be satisfactory in previous tests. For a similar reason, the tests conducted at RT were not necessary.

These mechanical tests demonstrated that:

1. the Lumbar I/F Cage component had loading properties at least as good as allograft bone; and
2. the two versions of the Lumbar I/F Cage component were mechanically equivalent to each other.

10.1.2 VSP Spine System component testing summary

Bilateral VSP Spine System component constructs were assembled (2 longitudinal elements, 4 pedicle screws and the appropriate interconnecting and locking components). These assemblies were placed into a test machine such that compression bending and torsional loading tests could be performed. The test configuration, load application and data collection were done in accordance with a method similar to that described in ASTM PS5-94, now known as ASTM F-1717.

Static and fatigue testing of bilateral constructs utilizing 4th generation pedicle screws

static bending stiffness (kN-m/m)	extension	25.9 ± 1.6
	flexion	34.4 ± 1.8
static bending strength (N-m)	extension	55.4 ± 3.5
	flexion	740.0 ± 25.9
static torsional stiffness (N-m/°)	internal rotation	4.5 ± 0.09
	external rotation	4.35 ± 0.19
static torsional strength (N-m)	internal rotation	16.1 ± 0.5
	external rotation	16.4 ± 0.5
dynamic bending moment (N-m)		39.5 @ 5 x 10^6 cycles

Based on these results, the VSP Spine System containing the 4th generation Stainless Steel AcroMed Pedicle Screws demonstrated adequate static and dynamic mechanical properties to resist the expected *in vivo* loads.

Static and fatigue component cantilever bending tests comparing the 4th generation screws to the 5th generation screws:

bending stiffness (kN-m/m)	4th gen.	14.74 ± 1.08
	5th gen.	17.18 ± 1.64
maximum moment (N-m)	4th gen.	30.93 ± 0.31
	5th gen.	39.91 ± 0.99
bending strength (N-m)	4th gen.	29.53 ± 0.19
	5th gen.	36.12 ± 2.04
dynamic bending moment (N-m)	4th gen.	6.11 @ 5 x 10^6 cycles
	5th gen.	7.97 @ 5 x 10^6 cycles

Based on these mechanical testing results, the 4th and 5th generation Stainless Steel AcroMed Pedicle Screws were determined to have similar mechanical behavior.

10.1.3 Summary of physical and chemical analyses

In order to further analyze the comparability of the two versions of the Lumbar I/F Cage component, physical and chemical analyses were performed. Samples of PEKEKK were also analyzed. These tests consisted of the following:

1. bulk Fourier transform infrared (FTIR) spectroscopy;
2. bulk energy dispersive x-ray (EDX);
3. scanning electron microscopy (SEM);
4. SEM/EDX;
5. thermogravimetric analysis and gas chromatography/mass spectometry (TGA-GC/MS).

Expected differences, *e.g.*, a higher concentration of PEKEKK, a smoother surface and a lower number of exposed fibers in the version of the I/F Cage with 70% polymer matrix, based on material analyses were confirmed. No unexpected differences were observed.

10.2 Standards

10.2.1 Performance standards

No performance standards exist for either the individual device components or the materials used in the manufacture of the Lumbar I/F Cage with VSP Spine System.

10.2.2 Voluntary standards

ASTM standards exist for the chemical composition of the grades of stainless steel (ASTM F-138, F-1314 and F-899-94) used to manufacture the VSP Spine System component and the surgical instruments. There are no voluntary standards for the Lumbar I/F Cage material.

Biomechanical tests were conducted according to ASTM provisional test methods (ASTM PS5-94, now known as ASTM F-1717) on the VSP Spine System component.

10.3 Summary of Non-clinical Studies

10.3.1 Biocompatibility

The following short term biocompatibility tests were performed on the composite used to make Lumbar I/F Cage components.

Pyrogenicity:	Limulus Amebocyte Lysate (LAL) Assay
Cytotoxicity	Agar Overlay and MEM Elution Assay
Mutagenicity:	Ames Test, In Vitro Mammalian Transformation, Unscheduled DNA Synthesis Assay and CHOHGPRT Gene Mutation Study
Systemic Toxicity:	Systemic Injection Test
Irritation Test:	USP XXII Intracutaneous Test
Sensitization Assay:	Maximization Test in Guinea Pigs
Carcinogenicity:	24 month Rat Implantation

Biocompatibility analyses were also performed on the version of the Lumbar I/F Cage described in the final PMA submission, as well as the version of the I/F Cage used in the US clinical trial. Specimens had either been steam sterilized (both version sof the I/F cage) or gamma irradiated (PMA version only). All tests were in accordance with International Organization for Standardization (ISO) 10993 and included ISO Muscle Implantation Study in the Rabbit with Histopathology (2 weeks and 4 weeks); ISO Sensitization Study in the Guinea Pig (Maximization Method); Mouse Bone Marrow Micronucleus Test; and *in-vitro* Mammalian Cell Gene Mutation Testing. All studies indicated that the base polymer (PEKEKK) and the polymer/carbon fiber composite material performed consistent with other biocompatible materials.

10.3.2 Functional Biocompatibility

In addition to the raw material biocompatibility testing performed in the *in vitro* and *in vivo* studies described above, a functional biocompatibility study was performed in goats. The Lumbar I/F Cage components used in this study consisted of 30% fiber/70% polymer, the same as in the US clinical trial. The objective of this study was to determine

fusion success, biocompatibility of the composite material and the possibility of carbon wear debris at intervals after surgical implantation. None of the animals were implanted with the VSP Spine System components.

Twenty-six Spanish goats had interbody lumbar fusion surgery in a randomized protocol. Fifteen goats were implanted with the I/F cage packed with autologous bone, and 11 goats were implanted with ethylene oxide-sterilized allograft bone.

At 6 months, one of three allograft implantations showed histologic and radiographic fusion, whereas five of five carbon fiber-reinforced polymer cage fusions showed at least partial fusion (*i.e.*, fusion present , but not across the entire disc space). At 12 months, two of three allograft implantations and five of five carbon fiber-reinforced polymer cage fusions were solidly fused. At 24 months, five of five allograft implantations and two of two carbon fiber-reinforced polymer cage implantations were solidly fused.

Histology was performed on samples containing the I/F Cages and fusion mass from the goats. Device debris, as well as isolated carbon fibers were noted at all time points evaluated. Fibrous tissue was present around the I/F Cage struts. No acute inflammation was observed in any sections.

Two factors were proposed as contributing to the formation of wear debris. First, the implants were not ultrasonically cleaned prior to implantation. This could leave loose particles and fibers remaining from the device manufacture on the surface. Second, because of the type of loads that were applied by the goats (more shear than compression compared to primarily compression in human use of the device) and the lack of additional stabilization which would have been produced by the VSP Spine System component, micromotion may have been present. This is supported by the location of the fibrous tissue, *i.e.*, around the I/F Cage struts. After these tests were conducted, ultrasonic cleaning was instituted for all I/F Cages.

Although debris was present, it did not produce tissue necrosis (in particular, the adjacent vertebral bone was not altered) and it did not appear to spread beyond the immediate area of the implant. From both of these factors, along with the expected reduction of *in vivo* shear loads in the human clinical setting and the additional stability which would be produced by the use of the VSP Spine System as one of the components of the device in the human clinical trial, the I/F Cage was believed not to present the potential for biocompatibility problems.

10.3.3 Human Histology

To date, retrieved I/F Cages or biopsies from the areas around the I/F Cages from eight patients have been histologically evaluated. These tissues were retrieved between 12 and 66 months after implantation. Some particles, that appeared to be device debris, were present; all of which were surrounded by fibrous tissue. Some macrophages containing

debris were also present. This biological response is similar to that seen from other orthopaedic devices and did not raise any concerns that the Lumbar I/F Cage component was not biocompatible. As a result, additional tests were not necessary.

11.0 Summary of Clinical Studies

11.1 Reports from Non-sponsor Investigations

Two reports (1 abstract and 1 article) described the use of a device similar to the Lumbar I/F Cage with VSP Spine System for several indications. Neither report identified adverse events that were not observed in the US clinical trial. In addition, the limited reported clinical results were comparable to those reported in the clinical trial.

11.2 Summary of Prospective IDE Study

11.2.1 Study Background

Clinical data to support the safety and effectiveness of the Lumbar I/F Cage with VSP Spine System were collected as part of an FDA-approved investigational device exemptions (IDE) clinical trial (IDE G900258). The original IDE consisted of 4 study arms as follows:

1. a prospective, randomized arm with concurrent controls to evaluate recurrent disc pathology ($n_{proposed}$ = 240, n_{actual} = 33 [19 investigational and 14 control]);
2. a prospective, randomized arm with concurrent controls to evaluate spondylolisthesis ($n_{proposed}$ = 240, n_{actual} = 27 [15 investigational and 12 control]);
3. a prospective, non-randomized arm with literature controls to evaluate multiple level disease ($n_{proposed}$ = 120, n_{actual} = 80 [44 DDD and 36 spondylolisthesis]);
4. a prospective, non-randomized arm with literature controls to evaluate multiple previous failed surgery and failed fusion; and ($n_{proposed}$ = 120, n_{actual} = 107 [49 DDD and 58 failed fusion]).

Patient enrollment for each of the proposed arms of the clinical trial was never completed. There were sufficient data from the DDD populations, however, to evaluate a PMA for this device. These combined, prospective data were obtained from the DDD patients from arm 1 (n = 19 randomized patients), arm 3 (n = 42 non-randomized patients) and arm 4 (n = 49 non-randomized patients).

The inclusion criteria for the DDD population were as follows: males and females between the ages of 18 and 89 with persistent back and/or leg pain refractory to 6 weeks of non-surgical therapy; a diagnosis of DDD at one, two, three or four levels of the lumbar spine; degenerative changes or herniation of the disc at the affected level(s) with or without instability as confirmed by appropriate imaging studies. The exclusion criteria

included significant osteoporosis or metabolic bone disease; past or present infection in the disc or the spine; tumor; spondyloptosis; past or present illicit drug abuse and current alcohol abuse; and clinically significant abnormalities at more than three levels. Because the DDD patients presented in the PMA were pooled from different study arms, additional inclusion/exclusion criteria may also have been applied, *e.g.*, multiple spinal level involvement for the patients in arm 3 or one or more previous non-fusion surgeries at the involved spinal level(s) for patients in arm 4.

Because of an inadequate number of prospective, randomized control patients, historical literature (as previously approved for the non-randomized arms) was used as the control population. All articles are listed in the Bibliography section at the end of this document. The control articles were selected by using three methods:

1. An initial set of articles relating to spinal fusion consisted of those that were referenced frequently in the literature. Articles from this group that more closely matched the IDE protocol and resultant submitted patient database, evaluation criteria and timepoints were kept as part of the control population.

2. A second set of articles was selected by performing searches in the Medline database using the search terms "posterior lumbar fusion", "posterior lumbar interbody fusion", "lumbar recurrent disc disease", "treatment of failed lumbar back", "multiply operated lumbar" and "degenerative disc disease". As with the first group of articles, those not closely matching the parameters of the IDE protocol and submitted patient population were excluded from the control population. This set of articles matching the search terms and the study and database parameters was identified in the original PMA submissions

3. The third set of articles was selected using the same Medline keyword criteria as the second method with the addition of limited publication dates. Only articles published between 1996 and 1998 were collected. This third method was used to supplement the literature control population after the initial submission of the PMA.

All patients were treated with the Lumbar I/F Cage with VSP Spinal System. The Lumbar I/F Cage component was filled with autologous cancellous bone. Post-operative care included use of external immobilization for the first month; avoidance of bending, lifting, stooping and twisting for the first 3 months; and avoidance of heavy lifting for the first 6 months.

Patients were evaluated pre-operatively and at 1, 3, 6, 12 and 24 months post-operatively. Evaluations were also made biennially after the 24 month follow-up evaluation. Complications and adverse events, device-related or not, were evaluated over the course of the clinical trial. At each evaluation timepoint, fusion status, pain, function and neurological status were evaluated. Success was determined from data collected during the initial 24 months of follow-up.

A pooling analysis was performed to assess the ability to pool data across investigational sites, between the indications originally used to describe the DDD patients in arms 1, 3 and 4 and across the number of levels treated. The pre-operative evaluations, 24 month follow-up evaluations and demographic data were utilized. While some statistically significant differences were identified, these were determined not to be clinically significant.

11.2.2 Effectiveness Analyses

The effectiveness variables included assessing fusion at the involved levels, pain, function, and neurological status (muscle strength). Data for all effectiveness variables were not available for all patients at all time points. Tables describing the success rates for all effectiveness variables are presented in section 11.2.4 below.

11.2.2.1 Effectiveness Analysis - Fusion

Fusion was evaluated using plain radiographs (standing views only, flexion/extension views were not taken). The radiographs were not assessed by an independent radiologist. Only the interbody fusion portion of the 360° fusion was assessed as part of the effectiveness analysis. The fusion mass was assessed using a seven point descriptive rating scale. Ratings of 1-4 were various descriptions of pseudarthrosis. A rating of 5 was used to describe "bone bridging fusion area"; a rating of 6 was used to describe "increased density of fusion bone" and a rating of 7 was used to describe "continuous trabecular bone bridging fusion". A fusion rating of 6 or 7 was considered to be indicative of fusion (success).[1]

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[1] Although the Lumbar I/F Cage® component is radiolucent and bone can be visualized through it, radiographic assessments of fusion are still imprecise and subjective. Because flexion/extension views were not taken, the fusion assessment was based solely on the investigator's subjective assessment of the quality and quantity of the fusion mass.

This was recognized as a concern by the sponsor in the investigational protocol, particularly in relation to the fusion rating of 5. Because well-packed bone graft could appear as bone bridging the fusion area immediately post-operatively (and was obviously not a solid fusion mass), investigators were prohibited from scoring fusion ratings of 5 as successes prior to the 12 month follow-up evaluation. In view of this, the Orthopaedic and Rehabilitation Devices Advisory Panel (the Panel) suggested that only a rating of 7 would indicate solid fusion. This is in contrast to the sponsor's presentation of fusion rating 5, 6 or 7 being indicative of fusion.

In order to address this concern, the sponsor provided evaluations of direct fusion mass manipulation. Patients who had a subsequent surgical intervention related to removal of the VSP® Spine System component had their fusion assessed radiographically prior to surgery. During surgery, the fusion mass was directly manually manipulated for assessment of bony fusion status. The pre-removal radiographic fusion scores were compared to the manual assessments.

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11.2.2.2 Effectiveness Analysis - Pain

Pain was measured on a five point scale where 1= "Pain is excruciating and unbearable", 2= "Pain is severe causing marked limitation of activities", 3= "Pain is moderate, causing limitation of activities", 4= "Pain is mild and may limit strenuous activities", 5= "No Pain".

Pain was recorded for 5 locations: Back, right leg, left leg, graft donor site and overall. Overall pain was used for the pain analysis. An increase in the pain assessment score indicates reduction in the patient's pain. All patients improving by at least one point between their pre-operative and their post-operative pain at 24 months would be considered to have had a successful result in terms of pain outcome measure. This distribution of overall pain scores preoperatively and at 24 months is shown below:

Pain Level		Pre-Operative Rate	24 Month Rate
None	(=5)	1.8% (n=2)	25.0% (n=23)
Mild	(=4)	0.9% (n=1)	41.3% (n=38)
Moderate	(=3)	14.5% (n=16)	26.1% (n=24)
Severe	(=2)	63.6% (n=70)	6.5% (n=6)
Excruciating	(=1)	19.1% (n=21)	1.1% (n=1)

11.2.2.3 Effectiveness Analysis - Function

Function was measured on a five point scale where 1= Total incapacity, 2= Able to do activities of daily living at home but unable to participate in social activities outside the home, 3= Able to participate in social activities outside the home but some activities significantly limited due to pain, 4= Able to do most regular social and recreational activities but with occasional recurrences of back pain or sciatica, 5= Able to do all social and recreational activities including sports, without pain.

An increase in the function assessment score indicates an improvement in the patient's function. All patients who maintained their function or improved it by at least one point between their pre-operative function and their post-operative function at 24 months

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While the two assessments were generally complementary, *e.g.*, the majority of patients rated as a 5 radiographically, were found to be fused as a result of direct manipulation, the direct manipulation results were from a potentially biased data source. In order to reduce the potential for misdiagnoses of pseudarthrosis and not rely on a potentially biased dataset, FDA utilized a fusion success rating of 6 or 7 instead of a success rating of 5, 6 or 7.

would be considered to have had a successful result in terms of function outcome measure. The table below shows the successful function rates for each study subgroup.

Function Level		Pre-Operative Rate	24 Month Rate
Full activity	(=5)	0 (n=0)	20.7% (n=19)
see text	(=4)	0 (n=0)	38.0% (n=35)
see text	(=3)	37.3% (n=41)	32.6% (n=30)
see text	(=2)	54.5% (n=60)	7.6% (n=7)
Total incapacity	(=1)	8.2% (n=9)	1.1% (n=1)

11.2.2.4 Effectiveness Analysis – Neurological Status (Muscle Strength)

Neurological status during the clinical trial was described in the submitted PMA database. It consisted of an evaluation during a physical examination which consisted of assessments of reflexes, sensation, straight leg raises and muscle strength. For the purposes of determining success, the analysis of neurological status focused on the evaluation of muscle strength. Reduced or impaired reflexes or sensations were reported as complications/adverse events.

Neurological status (muscle strength) was evaluated bilaterally for ten muscle groups: Hip Flexors, Hip Abductors, Quadriceps, Hamstrings, Ankle Dorsiflexion, Ankle Plantarflexion, Peroneal Muscles, Toe Flexors, Toe Extensors, and Extensor Hallucis Longus. Each muscle group was rated using a 6 point scale ranging as follows: 0=No movement, 1= Flicker or trace of contraction, 2= Active movement when gravity removed, 3= Active movement against gravity, 4= Active movement against gravity and resistance, and 5= Normal power. The majority of patients (59.7% = 132 /221) demonstrated normal muscle strength (all muscle groups rated 5) preoperatively.

All patients experiencing a decrease between their pre-operative muscle strength and their post-operative muscle strength at 24 months would be considered to have been a failure in terms of neurological status (muscle strength).

11.2.3 Safety Analysis

The complete list of complications, adverse events and subsequent interventions was listed previously in Section 7.0.

A multivariable analysis of the data demonstrated that certain events could be attributed to identifiable factors:

1. **Blood loss** was higher inpatients who had more spinal levels treated. This parameter was also investigator-dependent.

2. **Operative time**, as expected, increased as more spinal levels were treated. This parameter was also investigator-dependent.

3. **Dural tear rate** was dependent on the number of previous spinal surgeries at the involved levels.

4. **Removal of the VSP Spine System component** was higher for smokers (although the clinical significance of this correlation is not known). While not statistically significant ($p < 0.1$), there was a trend that this parameter was investigator-dependent.

11.2.4 Study Success/ Statistical Differences

To be considered an overall success[2], a patient must have met each of the following six criteria:

1. interbody fusion of the cage treated level(s);
2. improvement in overall pain;
3. maintenance or improvement in function;
4. maintenance or improvement in muscle strength;
5. no serious or permanent complication; and
6. no revision at the cage treated level.

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[2] Prior to deciding on this definition of overall clinical success, FDA reviewed two other definitions. In the submitted PMA database presented to the FDA, overall success was originally defined as a patient meeting all of the following criteria:

1. fusion of the cage treated level as defined by a fusion rating of 5, 6, or 7;
2. pain success defined as improvement in overall pain (with site specific pain evaluated, but not used in the evaluation of pain success);
3. function improved from pre-op levels if impaired, otherwise function maintained;
4. maintenance or improvement in neurological status (muscle strength);
5. no removal of the Lumbar I/F Cage component allowed, but removal of VSP Spine System component allowed if removal relieves pain; and
6. no serious or permanent complications.

As a result of their deliberation, the Panel recommended the following success definition:

1. fusion defined by a fusion rating of 7;
2. improvement in site specific pain and in overall pain;
3. maintenance or improvement in function;
4. maintenance or improvement in neurological (muscle strength) status;
5. no removal of the cage component and no removal of VSP Spine System component, even if removal of this component relieves pain; and
6. no serious or permanent complications.

Success rates for the individual outcome parameters and the overall success were analyzed two ways. The first analysis utilized only the available data from patients who had returned for their 24 month follow-up evaluation (92 patients out of the total DDD population of 110 patients). The second analysis utilized an intent-to-treat evaluation which assumes that all patients who were lost-to-follow-up at the 24 month evaluation are failures. The 7 DDD patients who died during the course of the clinical trial are not counted in the denominator as part of this type of analysis. This results in an expected 24 month DDD patient population of 103 patients.

	Available data		Intent-to-treat		Literature controls
parameter	n[α]	% (CI)[β]	n	% (CI)	% (CI)
fusion[χ]	82/91	90 (84, 96)	82/103	80 (72, 87)	84 (81, 87)
pain	81/92	88 (81, 95)	81/103	79 (71, 87)	76 (63, 87)
function	89/92	97 (93, 100)	89/103	86 (80, 93)	93 (77, 99)
muscle strength	85/92	92 (87, 98)	85/103	83 (75, 90)	100 (88, 100)
overall success	67/91	74 (65, 83)	67/103	65 (56, 75)	59 (49, 69)

[α]One patient did not have radiographic data at the 24 month follow-up evaluation, but had all other information.

[β]CI = 95% confidence interval

[π]Success rate provided for literature controls is a weighted average of values presented in articles. The weighting factor was the number of patients reported in each article.

[χ]The fusion success rates are based on assessments of only the interbody fusion mass.

A longitudinal analysis demonstrated that patients with worse pain and function preoperatively had a better chance of clinical success postoperatively.

11.2.5 Comparison with Literature Controls

A total of 33 articles were used as historical controls. These articles reported results of spinal fusion surgery that used PLIF and posterolateral fusions. Instrumented and non-instrumented fusions were described. While very few articles exist that exactly matched the IDE study population or study design, efforts were made to extract clinical and complication information for the purposes of comparison. The clinical outcomes and success rates (weighted averages and 95% confidence intervals) from the literature are presented in previous sections.

12.0 Conclusions drawn from studies

All of the data provided in the previous sections describing the pre-clinical, biomechanical and clinical studies provide reasonable assurance of the safety and effectiveness of the Lumbar I/F Cage with VSP Spine System when used by well-trained surgeons via an open, posterior approach for the treatment of DDD using autograft bone

at one or two spinal levels from L2-S1 in patients whose condition requires the use of interbody fusion combined with posterolateral fusion, in conjunction with posterior pedicle screw fixation, and who may have had previous non-fusion surgery at the same spinal level(s).

13.0 Panel Recommendation

The Panel met on December 11, 1997 to discuss this application. Based on the data presented, the Panel recommended against approval of the Lumbar I/F Cage with VSP Spine System.

The Panel discussed several issues which resulted in this recommendation:

1. The device evaluated in the clinical trial was not the same as the device presented in the PMA. The Lumbar I/F Cage component evaluated in the clinical trial, although composed of the same fiber and polymer matrix components as the device presented in the PMA, utilized these components in different ratios. There was concern that this would modify the surface of the implant and result in altered biocompatibility (*e.g.*, the impact of fewer fibers on the surface of the I/F Cage component, etc.) and altered biomechanics (*e.g.*, fatigue behavior, wear debris generation, etc.). Similar concerns were raised about design modifications that had occurred with the Stainless Steel AcroMed pedicle screw component.

2. Several adverse events, most notably dural tear rate, blood loss and removal of VSP Spine System components, were viewed as having rates or values that were too high. In addition, an adequate covariate analysis was not available to assess the relationships between treatment indications and certain adverse events.

3. Although the use of a posterolateral fusion was an option to the required interbody fusion, the majority of the patients received both fusions. Data were not presented for the two individual fusion groups and, therefore, the impact and outcomes of the different fusion treatments was unknown.

4. While the sponsor presented data for fusion success equals a fusion rating of 5, 6 or 7, the Panel believed that a fusion rating of 7 may have been more appropriate. Similar arguments were made for alternate, more conservative, definitions of pain and overall success.

5. Because of the invasiveness of the surgical approach, the Panel questioned the suitability of the device for the treatment of primary diseases and diseases with less extensive involvement, *e.g.*, single level surgery. There was a concern that the safety profile may not be appropriate for these populations.

6. There was some concern over the poolability of certain populations within the IDE's database.

7. Finally, the Panel provided some preliminary advice as to the contents of the device's labeling, *e.g.*, the need for surgeon training and an adequate description of the complications and indications.

14.0 CDRH Decision

CDRH agreed with the Panel's recommendations. On March 11, 1998, CDRH issued a not approvable letter for the Lumbar I/F Cage with VSP Spine System. This letter identified six questions that the sponsor needed to address in order for the device to be considered to be in an approvable state.

In response to this letter and a subsequent meeting with FDA (August 3, 1998), the sponsor submitted two major amendments to the PMA (dated May 4, 1998 and August 24, 1998). These amendments contained reanalyses and presentations of data previously submitted, as well as results from additional pre-clinical tests, descriptions of the European experience with the device, analyses and presentation of clinical information not previously submitted and supplemental literature control articles (articles published in the period since the initial PMA submission).

The submitted information supporting the determination of safety and effectiveness was divided into two main areas, preclinical data and clinical data.

14.1 Pre-clinical data

14.1.1 Mechanical testing

These tests were performed separately on the two components comprising the Lumbar I/F Cage with VSP Spine System. The version of the I/F Cage component used in the US IDE clinical trial was tested initially. Its baseline static compression and shear properties were compared to that of allograft bone. The I/F Cage component was then subjected to fatigue loading. The version of the I/F Cage component described in the PMA was subjected to identical loading conditions (static and fatigue). In addition, the two versions of the I/F Cage component were evaluated for the impact of loading environment (solution, *i.e.*, air, distilled water and soybean oil, and temperature, *i.e.*, room temperature and body temperature) on fatigue behavior.

These tests demonstrated that the I/F Cage component has mechanical properties at least as good as allograft bone and that the two versions of this component were mechanically equivalent to each other. As a result, relative mechanical safety had been established for this device component.

Static and fatigue tests were also performed on the VSP Spine System component to evaluate the design changes between the 4th generation of the AcroMed Pedicle Screw component of the VSP Spine System component (the version of this component used in the clinical trial) and the 5th generation of the AcroMed Pedicle Screw component of the VSP Spine System component (the version of this component in the PMA). From these tests, it was demonstrated that the 4th and 5th generation components had equivalent mechanical behavior. As a result, the relative mechanical safety had been established for this component of the device as well.

Because the two components of the Lumbar I/F Cage with VSP Spine System were determined to be individually mechanically safe, it was not necessary to perform tests on the components combined into a single device construct, as would be surgically implanted. As a result, relative mechanical safety for the complete Lumbar I/F Cage with VSP Spine System had been established.

14.1.2 Physical and chemical analyses

In addition to the mechanical tests described above, the two versions of the I/F Cage component were evaluated physically and chemically. As with the mechanical tests, these analyses confirmed the pre-clinical equivalence of the two versions of this component and added to the analysis of relative safety.

14.1.3 Biocompatibility testing

Because of it long history of use in heavily loaded, implantable orthopaedic spinal devices, the stainless steel used to manufacture the VSP Spine System component was not evaluated for biocompatibility. Its safety in this area has already been established. The material used to manufacture the I/F Cage component, on the other hand, was subjected to biocompatibility analyses. Both versions of this component were subjected to tests in accordance with ISO 10993 and each was determined to be biocompatible.

14.1.4 Functional biocompatibility (animal) testing

In addition to the cell culture and small animal evaluations described by ISO 10993, functional biocompatibility tests were performed. The I/F Cage component was implanted into goats, which were sacrificed at various time points post-implantation and analyzed histologically. No evidence of biocompatibility problems were observed.

14.1.5 Human histology

Histology was also performed on I/F Cage components that had been retrieved at various times post-implantation from 8 patients. The biological response observed from these analyses were similar to those seen for other orthopaedic implants and did not raise any new safety concerns relative to the biocompatibility of the I/F Cage component.

14.2 Clinical data

Two sets of data describing clinical experience with the device were reviewed. The first set described non-US experience, while the second set described the US IDE clinical trial experience.

14.2.1 Non-US clinical experience

The sponsor provided data from their experience with a version of the device used outside of the US. These data were not collected as part of any organized clinical trial. They were collected retrospectively on a version of the device that was similar to that described in the PMA. Because of the differences between the device proposed in the PMA and the device described in the non-US clinical experience, as well as an incomplete retrospective dataset and the lack of prospective data, the data from the European experience would not provide a direct comparison to the US clinical trial experience.

The European experience data were examined, however, to get a wider view of the relative safety of the Lumbar I/F Cage with VSP Spine System. From this analysis, it was observed that there were no different or additional safety concerns related to the use of these versions of the Lumbar I/F Cage with VSP Spine System than were already observed in the US clinical trial.

14.2.2 US IDE experience

As described above, the device evaluated in the US clinical trial differed from that proposed in the PMA. Pre-clinical testing established the mechanical, physical and chemical equivalence and the relative safety (mechanical and biocompatibility) of the two device versions. The non-US clinical experience (device similar to that proposed in the PMA) and the limited reports in the literature identified no differences in adverse events between the two versions of the device compared to that seen in the US clinical trial.

The clinical evaluation of safety and effectiveness for the clinical trial focused on poolability of the various study arms, reported complications/adverse events. the type of fusion performed, removal of the VSP Spine System components and definitions of success for some of the individual outcome parameters, as well as overall success.

The sponsor demonstrated that patients with 1 or 2 involved spinal levels could be pooled and analyzed together. They were also able to demonstrate that certain associated diagnostic groups from the original IDE could be pooled to form a single indication. These issues did not alter the device's safety or effectiveness.

The analysis of the safety data focused on whether certain parameters, most notably estimated blood loss, operative time, dural tear rate and removal of the VSP Spine System components deleteriously impacted the device's safety profile. These factors were found to be comparable to values reported in the literature, albeit at the higher end of the

reported ranges. Because of the nature of these concerns, CDRH believes that they could best be addressed in device labeling and the proposed surgeon training.

According to the clinical trial protocol, interbody fusions were required, but posterolateral fusions were optional. In practice, however, 90.5% of the total population received both fusion masses (a 360° fusion). As a result, all data represents the results from patients with 360° fusions. In addition, the fusion rates were only reported for the interbody portion of the fusion. The fusion rates for the posterolateral fusion mass were not reported and are not included as part of the assessment of the effectiveness of the Lumbar I/F Cage with VSP Spine System. Because of this, the Lumbar I/F Cage with VSP Spine System is only indicated for use with interbody fusion combined with posterolateral fusion.

While the clinical trial protocol did not require the removal of the VSP Spine System components, it did not prohibit it. In fact, the labeling of this component described the possibility of removal of these components after fusion had occurred. When this reason for removal was combined with removal due to component failure, the Panel believed that the removal rate was high. Reanalysis of these data by CDRH revealed that the reasons for removal appeared to fall into three relatively equal categories – removal after the determination of the presence of fusion, removal due to pain over the hardware and removal due to broken components. These corresponded to reasons reported in the literature. In addition, the removal rate reported for this device was within the range reported in the literature, albeit at the high end. CDRH believes that device labeling and surgeon training could address the issue of the possibility of a second surgical procedure to remove the VSP Spine System components.

The final area of concern focused on the definitions of overall success, specifically as it relates to the definition of pain success, the impact of complications on success and the definition of fusion success. The issues of overall success and pain success were addressed relatively easily.

In the clinical trial, three pain assessments were made - leg pain, back pain and overall pain. CDRH determined that overall pain was able to capture the relevant information in a simple manner. Pain success was, therefore, defined as improvement in overall pain compared to pre-operative levels.

In general, a device is evaluated both for safety and effectiveness. The success of a device, in this case the success rates for pain, function, neurological status, fusion and overall success, is the measure of its effectiveness. Safety is measured by an evaluation of complications and adverse events.

This general rule was followed during the evaluation of the Lumbar I/F Cage with VSP Spine System except for 6 patients in the total population of 221 patients (4 of these were DDD patients). For these patients, CDRH believes that the number and type of subsequent interventions were such that the patients should be considered clinical

failures. This is in contrast to the results of their 24 month evaluations, which categorized them as successes (for effectiveness). CDRH believes that these interventions should not have been considered routine or expected as part of the use of the Lumbar I/F Cage with VSP Spine System. In the overall success results described above, these patients were counted as overall failures. Their individual clinical outcome parameter scores, however, were not altered.

The final success definition relates to fusion. Fusion was evaluated using plain radiographs (standing views only, flexion/extension views were not taken) and assessed by a seven point descriptive rating scale. Ratings of 1-4 were various descriptions of pseudarthrosis. A rating of 5 was used to describe "bone bridging fusion area"; a rating of 6 was used to describe "increased density of fusion bone" and a rating of 7 was used to describe "continuous trabecular bone bridging fusion". Because of concerns about misdiagnoses of pseudarthrosis and relying on a potentially biased dataset (the manual manipulation results described above), a fusion success rating of 6 or 7 was utilized.

In view of these discussions, the data and analyses presented in the two major amendments and a number of minor amendments were sufficient to address the issues and questions raised by the Panel and FDA's March 11, 1998, not approvable letter. In addition, these data presentations and analyses reduced and focused the indications to the single one described above. As a result, CDRH believes that the sponsor has adequately demonstrated the safety and effectiveness of the Lumbar I/F Cage with VSP Spine System.

FDA inspections completed on November 17, 1998, determined the manufacturing facilities to be in compliance with the Good Manufacturing Practices (GMP) regulations.

CDRH issued an approval order on February 2, 1999.

15.0 Approval Specifications

Directions for Use: See labeling.

Hazards to Health from Use of the Device: See indications, contraindications, warnings, precautions and adverse events in labeling.

Post-approval Requirements and Restrictions: See approval order.

16.0 Bibliography

The following articles were used as the historical literature control for this PMA:

Biondi. J. and Greenberg, B.J., "Redecompression and Fusion in Failed Back Syndrome Patients," *J Spinal Disord,* 3:362-369, 1990.

Barr, J.S., *et al,* "Failed Surgery for Low-Back Pain and Sciatic Pain," *J Bone Joint Surg* Vol. 45-A, 1963.

Bridwell, K.H., *et al,* "The Role of Fusion in the Treatment of Degenerative Spondylolisthesis with Spinal Stenosis," *J Spinal Disord,* 6:416-472, 1993.

Carpenter, C.T., *et al,* "Repair of Pseudarthrosis of the Lumbar Spine," *J Bone Joint Surg,* Vol. 78-A:712-720, 1996.

Cleveland, M., *et al,* "Pseudarthrosis in the Lumbosacral Spine," *J Bone Joint Surg,* Vol. 30-A:302-313, 1948.

Cloward, R.W., "Spondylolisthesis: Treatment by Laminectomy and Posterior Interbody Fusion. Review of 100 Cases," C.O.R.R.,154:74-82, 1981.

Dennis, S., *et al,* "Comparison of Disc Space Heights after Anterior Lumbar Interbody Fusion," *Spine,* 14:876-878, 1989.

Ebeling, U., *et al,* "Microsurgical Reoperation Following Lumbar Disc Surgery, " *Neurosurgery,* 70:397-404, 1989.

Fandino, J., *et al,* "Reoperation after Lumbar Disc Surgery: Results in 130 Cases," *Acta Neurochir (Wien),* 122:102-104, 1993.

Finnegan, W.J., *et al,* "Results of Intervention in the Symptomatic Multiply Operated Back Patient," *J Bone Joint Surg,* Vol. 61-A:1077-1082, 1979.

Hanley, E.N. and Levy, J.A., "Surgical Treatment of Isthmic Lumbosacral Spondylolisthesis," *Spine,* 14:48-50, 1989.

Herkowitz, H.N. and Kurz, L.T., "Degenerative Lumbar Spondylolisthesis with Spinal Stenosis," *J Bone Joint Surg,* 73-A:802-808, 1991.

Hutter, C.G., "Posterior Intervertebral Body Fusion. A 25-Year Study," *C.O.R.R.,* 179:86-96, 1983.

Kaneda, K., *et al*, "Follow-up of Medial Facetectomies and Posterolateral Fusion with Instrumentation in Unstable Degenerative Spondylolisthesis," *C.O.R.R.*, 203:159-167, 1986.

Kim, S.S. and Michelsen, C.B., "Revision Surgery for Failed Back Syndrome," *Spine*, 17:957-960, 1992.

Kumar, A., *et al*, "Interspace Distraction and Graft Subsidence after Anterior Lumbar Fusion with Femoral Strut Allograft," *Spine*, 18:2393-2400, 1993.

Larsen, J.M, *et al*, "Assessment of Pseudarthrosis in Pedicle Screw Fusion: A Prospective Study Comparing Plain Radiographs, Flexion/Extension Radiographs, CT Scanning, and Bone Scintigraphy with Operative Findings," *J Spinal Disord*, 9:117-120, 1996.

Lehmann, T.R. and LaRocca, H.S., "Repeat Lumbar Surgery," *Spine*, 6:615-619, 1981.

Lenke, L.G., *et al*, "Results of In Situ Fusion for Isthmic Spondylolisthesis," *J Spinal Disord*, 5:433-442, 1992.

Lin, P.M., *et al.*, "Posterior Lumbar Interbody Fusion," C.O.*R.R.*, 180:154-168, 1983.

Mitsunaga, M.M., *et al.*, "Microscopically Assisted Posterior Lumbar Interbody Fusion," C.*O.R.R.*, 263:121-127, 1991.

O'Sullivan, M.G., *et al*, "Recurrent Lumbar Disc Protrusion," *Br J Neurosurg*, 4:319-326, 1990.

Pihlajamaki, H., *et al*, "Posterolateral Lumbosacral Fusion with Transpedicular Fixation," *Acta Orthop Scand*, 67(1):63-68, 1996.

Quimjian, J.D. and Matrka, P.J., "Decompression Laminectomy and Lateral Spine Fusion in Patients With Previously Failed Lumbar Spine Surgery," *Orthopedics*, 11:563-569, 1988.

Rechtine, G.R., *et al*, "The Efficacy of Pedicle Screw/Plate Fixation on Lumbar/Lumbosacral Autogenous Bone Graft Fusion in Adult Patients with Degenerative Spondylolisthesis," *J Spinal Disord*, 9:382-391, 1996.

Schwab, F.J., *et al*, "Effects of Spinal Instrumentation on Fusion of the Lumbosacral Spine," *Spine*, 20:2023-2028, 1995.

Stauffer, R.N. and Coventry, M.B., "Posterolateral Lumbar Spine Fusion. Analysis of Mayo Clinic Series," *J Bone Joint Surg*, 54-A:1195-1204, 1972.

Thalgott, J.S., *et al*, "Reconstruction of the Lumbar Spine Using AO DCP Plate Internal Fixation," *Spine*, 14: 91 –95, 1989.

Tullberg, T., *et al*, "Fusion Rate After Posterior Lumbar Interbody Fusion with Carbon Fiber Implant: 1-Year Follow-Up of 51 Patients," *Eur Spine J*, 5(3):178-82, 1996.

Verlooy, J., *et al*, "Failure of Modified Posterior Interbody Fusion Technique to Produce Adequate Pain Relief in Isthmic Spondylolytic Grade I Spondylolisthesis Patients," *Spine*, 18:1491-1495, 1993.

Waddell, G., *et al*, "Failed Lumbar Disc Surgery and Repeat Surgery Following Industrial Injuries," *J Bone Joint Surg*, 61-A: 201-207, 1979.

Wetzel, F.T. and LaRocca, H., "The Failed Posterior Lumbar Interbody Fusion," *Spine*, 16:839 –845, 1991.

Wood, G.W., *et al* , "The Efficacy of Pedicle Screw/Plate Fixation on Lumbar/Lumbosacral Autogenous Bone Graft Fusion in Adult Patients with Degenerative Spondylolisthesis," *Spine*, 20:819 –830, 1995.