SUMMARY OF SAFETY AND EFFECTIVENESS

1. General Information

Device Generic Name: Cervical Interbody Fusion Instrumentation

Device Trade Name: BAK/Cervical Interbody Fusion System

Applicant's Name and Address: Centerpulse Spine-Tech Division (formerly Sulzer Spine-Tech)
7375 Bush Lake Road
Minneapolis, Minnesota 55439

Date of Panel Recommendation: January 19, 2001

Premarket Approval (PMA) Application Number: P980048

Date of Notice of Approval: April 20, 2001

2. Indications for Use

The BAK/Cervical (hereinafter called the BAK/C) Interbody Fusion System is indicated for use in skeletally mature patients with degenerative disc disease (DDD) of the cervical spine with accompanying radicular symptoms at one disc level. DDD is defined as discogenic pain with degeneration of the disc confirmed by history and radiographic studies. BAK/C implants are used to facilitate fusion in the cervical spine and are placed via an anterior approach at the C-3 to C-7 disc levels using autograft bone.

3. Contraindications

BAK/C devices should not be implanted in patients with:

- an active infection
- an allergy to titanium or titanium alloy

4. Precautions

Surgeons should not implant the BAK/C Interbody Fusion System until receiving adequate training regarding the surgical technique. Inadequate training may result in poor patient outcomes and/or increased rates of adverse events. See the BAK/C Interbody Fusion System Surgical Technique Manual for more information on proper implantation technique.

No implant should be re-used if it has come in contact with human tissue or bodily fluid.

5. Device Description

The BAK/C Interbody Fusion System consists of implants and instrumentation designed specifically for implantation of these devices. The implants have the following design characteristics:

- Implants are machined from rolled stock titanium alloy (Ti-6Al-4V, ASTM F136).

- Each implant is a hollow, threaded cylinder. The leading thread of each device begins as a V-form thread and transitions to a flat modified square thread covering the entire outer surface of the implant. The threads have a pitch of 0.083". The device is conically tapered (28°) on its leading (posterior) edge. The trailing (anterior) edge has a threaded center hole with four pinholes designed to mate with the implant driver.
- Its surface is perforated with 0.1094" diameter holes which are machined through the device wall at angles between 10° and 15° off the central axis. The number of holes varies by implant diameter: there are 12 on the 6mm implant; 18 on the 8mm, 24 on the 10mm, and 30 on the 12mm.
- During preparation of the disc space, local bone fragments are collected inside the reaming instrument and are placed into the BAK/C implant in order to minimize the need for harvesting additional bone from the iliac crest.
- When implanted in pairs, the devices are placed 1mm apart from each other; when implanted singly, the implants are placed in the center of the disc space.
- The following implant sizes (minor diameter x length) are available:

part number	description
6000-0612-00	6 x 12mm implant
6000-0812-00	8 x 12mm implant
6000-1012-00	10 x 12mm implant
6000-1212-00	12 x 12mm implant

Note:The 6 and 8mm devices generally are implanted in pairs; the 10 and 12mm devices typically are implanted singly.

6. Alternative Practices and Procedures

Alternative surgical treatments include, but are not limited to, various bone grafting techniques (e.g., Cloward bone dowels, Smith Robinson tri-cortical wedges, and Keystone grafts) used in conjunction with anterior cervical discectomy with fusion (ACDF) procedures. These bone grafting techniques are sometimes reinforced with cervical plating.

Non-operative alternative treatments include, but are not limited to, medication including analgesics and muscle relaxants, heat, rest, transcutaneous nerve stimulation (TENS), traction, hydrotherapy, stretching and strengthening exercises, patient education, use of good body mechanics, local injections, braces, and chiropractic care.

7. Marketing History

The device has a marketing history in the following countries: Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Czech Republic, Denmark, Finland/Estonia, France, Germany, Greece, Hong Kong, Iceland, Italy, Japan, Luxembourg, Netherlands, Norway, Philippines, Poland, Portugal, Puerto Rico, Singapore, Slovenia, South Africa, Spain, Sweden, Switzerland, Taiwan, Turkey, United Kingdom, and Venezuela. The BAK/C has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

8. Adverse Effects of the Device on Health

A total of 164 BAK/C device patients and 134 anterior cervical discectomy and fusion (ACDF) patients were enrolled in a multi-center clinical study of the BAK/C Interbody Fusion System. In the BAK/C patient group, the most common adverse event was degeneration of an adjacent disc (6%). Other adverse events that occurred in at least 1% of the study population include: continuing or new symptoms (1.9%), degeneration of a non-adjacent disc (1.7%), dural tear

(1.3%), incision-related events (1.5%), pseudoarthrosis (1.5%), and vocal paresis (1.2%). See Table 1 for a summary of adverse event rates observed in the clinical study; events are listed in alphabetical order. A complication reported at multiple time points is indicated as one event and listed at the time of first report. The complication rates for each follow-up interval were calculated by dividing the number of patients experiencing a given complication by the total number of patients with available data. The cumulative complication rates in Table 1 were derived using survival analysis techniques. The product of the proportion of patients free from adverse events over each time interval resulted in the cumulative rates provided in the table.

For the adverse events described in Table 1, some patients required additional surgery to treat the complication. The most common of these events was degeneration of an adjacent disc (2.8%). Other adverse events requiring additional surgery in at least 1% of the study population include: degeneration of a non-adjacent disc (1.7%), pseudoarthrosis (1.5%). See Table 2 for a summary of the complications that led to surgical interventions subsequent to the clinical trial surgery.

Surgical interventions subsequent to the clinical trial surgery can also by stratified by the types of operations performed. These included *revision, removal, supplemental fixation,* and *reoperation*. See Table 3 for a summary of the types of additional surgeries that were conducted.

Table 1: Complications at Each Time Point (Unrestricted[1] Cohort)

	Operative Number (%)		Post-op (1 day to 1 ½ months) Number (%)		3-month (1 ½ months to 4 ½ months) Number (%)		6-Month (4 ½ months to 9 months) Number (%)		12-Month (9 months to 18 months) Number (%)		24-Month (greater than 18 months) Number (%)		Cumulative[2] Complication Rate % at 24-months	
	BAK/C n = 164	Control n = 134	BAK/C n = 154	Control N = 125	BAK/C n = 147	Control N = 118	BAK/C n = 116	Control n = 86	BAK/C n = 126	Control n = 94	BAK/C n = 101	Control n = 80	BAK/C	Control
Anesthesia-related	1 (0.6)	-	-	-	-	-	-	-	-	-	-	-	0.6	-
Continued/new symptoms	-	-	1 (0.6)	-	1 (0.7)	1 (0.8)	-	-	1 (0.8)	-	-	-	1.9	0.8
Degeneration/adjacent disc	-	-	-	-	-	-	3 (2.6)	1 (1.2)	2 (1.6)	4 (4.3)	3 (3.0)	-	6.0	4.7
Degeneration/non-adj. disc	-	-	-	-	-	-	-	-	1 (0.8)	-	1 (1.0)	-	1.7	-
Dural tear	-	-	-	-	1 (0.7)	-	1 (0.9)	-	-	-	-	-	1.3	-
Dysphagia	-	1 (0.7)	1 (0.6)	1 (0.8)	-	1 (0.8)	-	-	-	-	-	2 (2.5)	0.6	4.5
Implant/Graft collapse	-	-	-	3 (2.4)	-	3 (2.5)	-	1 (1.2)	-	2 (2.1)	-	-	-	6.3[3]
Graft migration	-	-	-	1 (0.8)	-	-	-	-	-	-	-	-	-	0.8
Incision related	-	2 (1.5)	1 (0.6)[4]	7 (5.6)[4]	-	-	-	-	-	-	1 (1.0)	-	1.5	6.9[5]
Increased instability	-	-	-	-	-	-	-	1 (1.2)	-	-	-	-	-	0.8
Myocardial infarction	1 (0.6)	-	-	-	-	-	-	-	-	-	-	-	0.6	-
Pneumonia	-	-	1 (0.6)	-	-	-	-	-	-	-	-	-	0.6	-
Pseudoarthrosis	-	-	-	-	-	3 (2.5)	1 (0.9)	2 (2.3)	1 (0.8)	1 (1.1)	1 (1.0)	-	1.5	4.9
Spinal stenosis	-	-	-	-	1 (0.7)	-	-	-	-	-	-	-	0.6	-
Thrombophlebitis	-	-	1 (0.6)	-	-	-	-	-	-	-	-	-	0.6	-
Vocal paresis	1 (0.6)	-	1 (0.6)	1 (0.8)	-	-	-	-	-	-	-	-	1.2	0.8
Other	-	1 (0.7)[6]	1 (0.6)[7]	1 (0.8)[8]	1 (0.7)[9]	-	-	-	-	-	1 (1.0)[10]		2.1	1.5
Total	3 (1.8)	4 (3.0)	7 (4.5)[11]	14 (11.2)[11]	4 (2.7)	8 (6.8)	5 (4.3)	5 (5.8)	5 (4.0)	7 (7.4)	7 (6.9)	2 (2.5)	16.9	25.3[12]

[1] See *Analysis Cohorts* in Section 11.e. for an explanation of the Restricted and Unrestricted Cohorts
[2] Based on Life Table analysis
[3] Overall cumulative difference statistically significant at 0.0014 using Wilcoxon (Gehan) statistical test
[4] Difference statistically significant at 0.024 using Fishers exact test
[5] Overall cumulative difference statistically significant at 0.0142 using Wilcoxon (Gehan) statistical test
[6] Laryngeal spasm: During extubation, patient developed laryngospasm that was treated with Lasix
[7] Paraspinous spasm: 3 days post-operatively, patient complained of pain and spasm which was treated with intravenous muscle relaxant
[8] Hematoma: 3 days post-operatively, patient complained of swelling in neck without signs of infection that was treated with 1 day course of Decadron and observation
[9] Nerve root compression: Patient reported arm pain. CT revealed adjacent level nerve root compression resulting from disc herniation; symptoms did not correlate with adjacent level disease
[10] Injury: Complained of increased cervical pain following involvement in altercation
[11] Difference statistically significant at 0.042 using Fishers exact test
[12] Overall cumulative difference statistically significant at 0.0178 using Wilcoxon (Gehan) statistical test

Table 2: Complications Requiring Additional Surgery (Unrestricted[1] Cohort)

	Post-op (1 day to 1 ½ Months) Number (%)		3-month (1 ½ months to 4 ½ Months) Number (%)		6-Month (4 ½ months to 9 months) Number (%)		12-Month (9 months to 18 months) Number (%)		24-Month (greater than 18 Months) Number (%)		Cumulative[2] Complication Rate % at 24-months	
	BAK/C n = 154	Control N = 125	BAK/C n = 147	Control N = 118	BAK/C n = 116	Control n = 86	BAK/C n = 126	Control n = 94	BAK/C n = 101	Control n = 80	BAK/C	Control
Continued/new symptoms	-	-	-	-	-	-	1 (0.8)	1 (1.1)	-	-	0.68	0.77
Degeneration adj. disc	-	-	-	-	1 (0.9	1 (1.2)	3 (2.4)[3]	3 (3.2)[4]	-	-	2.79	3.72
Degeneration non-adj. disc	-	-	-	-	-	-	1 (0.8)[3]	1 (1.1)	2 (2.0)	-	1.71	-
Implant/Graft collapse	-	1 (0.8)	-	1 (0.8)	-	1 (1.2)	-	2 (2.1)[4]	-	-	-	3.89[5]
Pseudoarthrosis	-	-	-	-	1 (0.9)	1 (1.2)	1 (0.8)	-	1 (1.0)	2 (2.5)	1.50	2.38
Spinal stenosis	-	-	-	-	1 (0.9)	-	-	-	-	-	0.62	-
Nerve root compression	-	-	1 (0.7)	-	-	-	-	-	-	-	0.62	-
Total	-	1 (0.8)	1 (0.7)	1 (0.8)	3 (2.6)	3 (3.5)	6 (4.8)	7 (7.4)	3 (3.0)	2 (2.5)	6.22	10.78

[1] See *Analysis Cohorts* in Section 11.e. for an explanation of the Restricted and Unrestricted Cohorts

[2] Based on Life Table Analysis

[3] A single patient experienced 2 separate events (9 months post-operative: adjacent level DDD; 16 months post-operative: disc herniation at a non-adjacent level)

[4] A single patient experienced 2 separate events (10 months post-operative: graft collapse revised with plate and allograft; 13 months post-operative: graft collapse with hardware failure treated with fibular strut, plating and halo application

[5] Cumulative difference statistically significant at 0.0121 using Wilcoxon (Gehan) statistical test

Table 3: Additional Surgery Categories (Unrestricted[1] Cohort)

	Post-op (1 day to 1 ½ Months) Number (%)		3-month (1 ½ months to 4 ½ Months) Number (%)		6-Month (4 ½ months to 9 months) Number (%)		12-Month (9 months to 18 months) Number (%)		24-Month (greater than 18 Months) Number (%)		Cumulative[2] Complication Rate % at 24-months	
	BAK/C n = 154	Control N = 125	BAK/C n = 147	Control N = 118	BAK/C n = 116	Control n = 86	BAK/C n = 126	Control n = 94	BAK/C n = 101	Control n = 80	BAK/C	Control
Revisions[3]	-	-	-	-	-	1 (1.2)	-	-	-	-	0.0	0.8
Removals[4]	-	-	-	-	1 (0.9)	-	-	-	-	-	0.6	0.0
Supplemental Fixation[5]	-	1 (0.8)	-	1 (0.8)	-	1 (1.2)	3 (2.4)	3 (3.2)	1 (1.0)	2 (2.5)	4.3	4.6
Reoperations[6]	-	-	1 (0.7)	-	2 (1.7)	1 (1.2)	2 (1.6)	4 (4.3)	2 (2.0)	-	2.9	8.8
Total	-	1 (0.8)	1 (0.7)	1 (0.8)	3 (2.6)	3 (3.5)	5 (4.0)[7]	7 (7.4)	3 (3.0)	2 (2.5)	6.22	10.78

[1] See *Analysis Cohorts* in Section 11.e. for an explanation of the Restricted and Unrestricted Cohorts

[2] Based on Life Table Analysis

[3] Revision = An operation that adjusts the implant configuration

[4] Removal = an operation that removes the implant is removed with or without replacing it

[5] Supplemental Fixation = an operation that implants an additional spinal device(s)

[6] Reoperation = an operation that does *not* remove, modify or add any implant components

[7] Total differs from Table 2 because a single patient had 1 Supplemental Fixation procedure to correct 2 complications (i.e., 1 report of pseudoarthrosis and 1 report of non-adjacent disc degeneration)

9. Potential Adverse Effects of the Device on Health:

The following is a list of potential adverse events which may occur with cervical interbody fusion surgery with the BAK/C Interbody Fusion System. Some of these events may have been reported previously in the adverse events tables.

- Disassembly, bending, breakage, loosening, and/or migration of components.
- Foreign body (allergic) reaction.
- Tissue or nerve damage.
- Post-operative change in spinal curvature, loss of correction, height, and/or reduction.
- Infection.
- Dural tears.
- Neurological system compromise.
- Dysphagia/dysphonia
- Scar formation.
- Bone fracture.
- Non-union (or pseudarthrosis), delayed union, mal-union.
- Cessation of any potential growth of the operated portion of the spine. Loss of spinal mobility or function.
- Graft donor site complications.
- Damage to blood vessels and cardiovascular system compromise.
- Gastrointestinal complications.
- Damage to internal organs and connective tissue.
- Development of respiratory problems.
- Incisional complications.
- Change in mental status.
- Death.

Note: Additional surgery may be necessary to address some of these potential adverse events.

10. Pre-Clinical Studies

This section provides summaries of preclinical tests performed on the BAK/C Interbody Fusion System. Table 4 describes the non-clinical studies and is divided into the following categories: Bench Testing and Animal Testing.

Finite Element Analysis (FEA) was conducted on all sizes of the BAK/C implant. From the FEA, Sulzer Spine-Tech determined that the 6mm implant represents the worst case construct. Therefore, 6mm implants were used to determine the ultimate strength of the device.

Table 4: Summary of Pre-Clinical Studies

Study	Results/Conclusions
Bench Testing	
Ultimate Static Strength, 6mm implant (ASTM draft F-04.25.02.02)	4929.16 ± 563.1N Therefore, the device should withstand anticipated loads in the cervical spine. NOTE: SST estimated the axial compressive load in the cervical spine based upon *in vivo* intradiscal pressures published in the literature by Hattori (1981). From Hattori's research , SST estimated the cervical intervertebral load to be 118.8 N. SST established a clinical load requirement of 356 N (80 lbs) by assuming a safety factor of three (i.e., 118.8 x 3 = 356.4)
Dynamic Compression Strength (ASTM draft F-04.25.02.02)	Implant survived 5 million cycles at 533.8 N. Therefore, the device should withstand anticipated loads in the cervical spine. See Note above.
***In Vitro* Flexibility and Stability** Testing was conducted on human cadaveric spines to determine any differences in spine stability due to the number of implants placed at a spinal level (i.e., one vs. two). Single and paired BAK/C implants were placed at C4-C5 and C6-C7 in 13 spines as follows: ▪ 6 single BAK/C implants at C4-C5 ▪ 5 paired BAK/C implants at C4-C5 ▪ 6 single BAK/C implants at C6-C7 ▪ 5 paired BAK/C implants at C6-C7	No statistically significant differences in range of motion, neutral zone, or average stiffness were found between construct groups (i.e., single vs. paired implants) with one exception – change in neutral zone for axial rotation. Therefore, there are no relevant differences in initial stability between the single or paired configurations of the BAK/C implant.
Animal Testing	
Goat Cervical Spine Model Three adjacent levels (C3-C6) were instrumented with one of the following: ▪ uncoated BAK/C with autograft (n=7 animals, 21 levels) ▪ HA-coated BAK/C with autograft (n=7 animals, 21 levels) Radiographs were taken at 1, 3, 6, 9, and 12 weeks. The animals were sacrificed at 12 weeks. The harvested spines were subjected to stability testing followed by histological analysis. Sagittal micro-radiographs were used to assess fusion.	No statistical differences were seen in the stability data. Fusion was observed as follows: ▪ 48% of the levels implanted with the uncoated BAK/C were fused ▪ 62% of the spinal levels implanted with the HA-coated BAK/C were fused
Sheep Cervical Fusion Model This study compared the following three constructs: ▪ BAK/C implant filled with autograft (n=3 animals, 6 levels) ▪ uninstrumented autograft iliac crest grafts (n=3 animals, 6 levels) ▪ autograft iliac crest grafts with anterior plating (n=3 animals, 6 levels) Radiographs were used to assess fusion.	Fusion rates were: ▪ 33% for the BAK/C group ▪ 67% for the autograft bone group ▪ 100% for the anterior plate group

11. Summary of Clinical Study

a. Study Design

The clinical study for the BAK/C Interbody Fusion System compared BAK/C implants to an anterior cervical discectomy and fusion (ACDF) surgical procedure for the treatment of cervical degenerative disc disease. The study was designed as an equivalence trial to evaluate the safety and effectiveness of the device in a prospective, randomized, multi-center, controlled investigation. The effectiveness measures selected for this investigation evaluated whether the affected disc level was fused, whether there was relief from neck pain and radicular symptoms (arm/shoulder pain, loss of muscle strength, sensation abnormalities) and whether there were improvements in patient function (physical and mental). Safety information was measured by an analysis of adverse event reports.

b. Inclusion/Exclusion Criteria

Patients were enrolled in this study according to the following inclusion/exclusion criteria:

Inclusion criteria

- Discogenic radiculopathy of the cervical spine at levels between C-3 and C-7
- Radicular symptoms (arm-shoulder pain, decreased strength, abnormal sensation, and/or abnormal reflexes)
- Discogenic origin of disease confirmed by radiographic analysis, including one or more of the following:
  - degenerated (darkened) disc on MRI
  - decreased disc height compared to adjacent normal discs on x-ray, CT or MRI,
  - disc herniation on CT or MRI
- Age between 18 and 65 years old

Exclusion criteria

- Systemic infections
- Significant metabolic bone disease (i.e., osteoporosis or osteomalacia)
- Circulatory, cardiac or pulmonary problems
- Active malignancy
- Non-discogenic cause of symptoms (e.g., cervical tumor)
- Degenerative disc disease of three or more cervical spine segments
- Previous fusion attempt at same level
- Acute cervical trauma and/or significant instability (i.e., subluxation >3mm on lateral flexion/extension x-rays)
- Rheumatoid disease of the cervical spine
- Moderate to severe myelopathy

c. Demographic Data

Two hundred ninety-eight (298) patients (164-BAK/C patients; 134-ACDF patients) were enrolled at 28 institutions in the United States. Of the patients enrolled, 48.7% were female and 51.3% were male; the mean age at enrollment was 44.1 years. A total of 45.1% patients experienced symptoms of cervical degenerative disc disease with radicular involvement for more than nine months prior to enrollment in the study; 34% had experienced symptoms for between 3 and 9 months; and 20.1% had experienced symptoms for less than 3 months. Compensation-related injuries accounted for 29.5% of

the study population. The study cohort was comprised of patients employed preoperatively (53.4%), patients unemployed and on disability (32.2%) and patients unemployed for other reasons (14.4%). A total of 40.2% of the study population were smokers preoperatively. There were no statistically significant demographic differences identified between the BAK/C and ACDF patients.

d. Treatment Protocol

Patients were randomized prior to surgery to the treatment (BAK/C device) or control (anterior cervical discectomy with fusion, ACDF) arm of the study. BAK/C patients received one or two devices at each spinal level intended to be fused. Autograft and/or allograft were placed into the BAK/C device(s) as part of the implant procedure to facilitate fusion. Patient follow-up examinations were performed post-operatively, and at 3, 6, 12, and 24 months after treatment. Follow-up examinations were conducted annually after the 24-month time point.

Outcomes Assessed and Success Criteria

- Fusion was assessed by independent review of lateral flexion/extension (F/E) and anterior/posterior (A/P) radiographs. Fusion success was defined as less than 4° of segmental movement on lateral flexion/extension x-rays with less than 2mm of radiolucent lines covering less than 50% of the implant's outer surface as visualized on AP and lateral x-rays.

- Neck pain status was determined by patient completion of a ten-point visual analog scale. Neck pain success was defined as at least a 2-point improvement in neck pain score in patients with a preoperative score of 4 or more, or maintenance of the preoperative score in patients with preoperative scores of 3 or less.

- Radicular signs and symptoms measured included arm-shoulder pain, muscle strength, and sensation status.

    - Arm-shoulder pain status was determined by patient completion of a ten-point visual analog scale. Arm-shoulder pain success was defined as at least a 2-point improvement in arm-shoulder pain scores in patients with preoperative arm-shoulder pain scores of 4 or more, or maintenance of the preoperative score in patients with preoperative scores of 3 or less. Both limbs must have met the respective success criterion.

    - Muscle strength status was determined by clinical assessment of the deltoid, biceps, and triceps muscles. Muscle strength success was defined as maintenance of or improvement in muscle strength for the deltoids, biceps, and triceps in both arms. Patients presenting with preoperative muscle weakness with pre-op neck and arm-shoulder pain scores of 3 or less must have experienced improvement in the affected muscle group.

    - Sensation status was determined by clinical assessment. Sensation success was defined as maintenance of or improvement in sensation response in both arms. Patients presenting with pre-op neck and arm-shoulder pain scores of 3 or less must have experienced an improvement in all preoperative sensory abnormalities.

- Function assessment consisted of Physical Component Summary Scales (PCS) and Mental Component Summary Scales (MCS) computed from patient responses to the SF-36 Health Survey. Function success was defined as maintenance of or improvement in both the Physical Component Summary Scales (PCS) and Mental Component Summary Scales (MCS) according to the algorithm in the SF-36 user's manual.

- Overall success was defined as successful outcomes for each of the four previously described study outcomes (fusion, neck pain, radicular signs and symptoms, and function) without the necessity for additional surgery for supplemental fixation, revision, replacement, or removal of BAK/C system or bone graft implant.

- Safety was assessed by completing adverse event reports for all reported complications, including complications requiring additional surgery, implant-related complications, and complications related to the surgical procedure. Safety success was defined as a complication rate for BAK/C that was *equivalent to* (i.e., no worse than) the complication rate experienced in patients receiving the ACDF procedure.

e. Analysis Cohorts

Two patient cohorts were identified for analysis. The first analysis cohort was a subset of the second, and was made up of all data available for patients that were due for follow-up as of November 1999, referred to as the "Restricted Cohort". The second analysis cohort was made up of all data available for patients due for follow-up as of June 20, 2000, referred to as the "Unrestricted Cohort". The proportion of patients with complete efficacy data in the Restricted Cohort was greater than that of the Unrestricted Cohort, thus, efficacy conclusions for the study are based on the results from the Restricted Cohort. In contrast to efficacy data, the proportions of patients with complete safety data collected from the Restricted and Unrestricted cohorts were comparable. In order to include all available safety data, safety conclusions for the study are based on the results from the Unrestricted Cohort.

Complete data from 18.7% of the Restricted Cohort was not available at the time of data analysis. To investigate the possible effect of missing data on the study conclusions, an additional analysis was conducted. This "sensitivity analysis" examined a hypothetical scenario in which missing data for ACDF patients showed better clinical results than actual ACDF data collected. The results of this analysis showed that all but one of the outcome measures were *not sensitive* to this hypothetical advantage. Only the neck pain success measure was sensitive to this hypothetical advantage.

f. Patient Accountability

As stated previously, patient follow-up examinations were performed immediately post-operatively, and at 3, 6, 12, and 24 months after treatment. For patients missing their 24-month evaluation, follow-up data were attempted to be collected at time points greater than 24 months. Any data collected after the 24-month follow-up interval were designated "24-month +" data. The "24-month" and "24-month +" evaluations were grouped and reported in the tables below as "Long-term" results.

Of the 164 BAK/C patients and 134 ACDF patients enrolled, complete safety and effectiveness data were not available for all patients at each follow-up examination.

Table 5 provides a summary of the number of patients who contributed complete safety data at each follow-up interval. Safety data were considered complete if the patient had a completed complication case report form and clinical assessments of fusion and neck pain. The safety analyses were performed on the cohort of all patients enrolled as of June 20, 2000. The denominator for each interval represents the number of patients due for that follow-up evaluation as of June 20, 2000. **Table 6** provides a summary of the number of patients who contributed complete effectiveness data at 6 and 12 months and at 24 months or later. (*Note: The study protocol did not require that complete effectiveness data be collected until the 6-month examination).* Effectiveness data were considered complete if the patient had clinical assessments of fusion, neck pain, radicular symptoms, and function. The effectiveness analyses were performed on the cohort of all patients due for follow-up as of November 17, 1999. The denominator for each interval represents the number of patients due for that follow-up evaluation as of November 17, 1999.

Table 5: Safety Data Accountability

Post-operative		3-month		6-month		12-month		Long-term[1]	
BAK/C x/n (%)	Control x/n (%)	BAK/C x/n (%)	Control x/n (%)	BAK/C x/n (%)	Control x/n (%)	BAK/C x/n (%)	Control x/n (%)	BAK/C x/n (%)	Control x/n (%)
154/164 (93.9)	125/134 (93.3)	147/164 (89.6)	118/134 (88.1)	116/164 (70.7)	86/134 (64.2)	126/161 (78.3)	94/131 (71.8)	101/144 (70.1)	80/118 (67.8)

[1] Follow-up examination conducted 24 months post-operatively or later

Table 6: Effectiveness Data Accountability

6-month		12-month		Long-term[1]	
BAK/C x/n (%)	Control x/n (%)	BAK/C x/n (%)	Control x/n (%)	BAK/C x/n (%)	Control x/n (%)
114/160 (71.3)	85/130 (65.4)	124/150 (82.7)	94/122 (77.0)	85/101 (84.2)	66/87 (75.9)

[1] Follow-up examination conducted 24 months post-operatively or later

g. Statistical Analysis

Safety and efficacy of the BAK/C implants were assessed through Bayesian statistical methods; however, classical statistical analyses were conducted to aid in the interpretation of the study results. The Bayesian approach is a method that can be used to directly address the question of equivalence. Study conclusions regarding both efficacy (outcome measures) and safety (adverse events) were made based on the pre-determined definition of equivalence, specifically, a log-odds advantage of -0.811. Thus, a 90% credible interval that is completely above +0.811 corresponds to a conclusion of superiority; a 90% credible interval that is completely above -0.811 corresponds to a conclusion of equivalence, and a 90% credible interval that contains -0.811 corresponds to a conclusion of no strong evidence for equivalence.

h. Effectiveness Analyses

The Bayesian analysis methods employed to assess safety and effectiveness combine data with a diffuse prior distribution to determine the posterior distribution of the parameters of interest. The posterior distributions of the parameter, in conjunction with certain contrasts of interest, form the basis for determination of success outcomes. The posterior

distribution can be summarized by 95% credible intervals. The lower and upper limits of this interval are such that 95% of the posterior distribution is contained between the lower and upper limits of this interval, 2.5% below the lower limit and 2.5% above the upper limit. The Bayesian analysis results presented in the following section provide the Bayesian study effectiveness results based on the patient population referenced in Table 6**.** The lower and upper limits of the posterior distributions of the difference in BAK/C and ACDF success rates are summarized for each of the success measures.

NOTE: The BAK/C clinical study included patients who received treatment at two adjacent levels. Data were collected from fifty-one (51) two-level BAK/C patients and twenty-eight (28) two-level ACDF patients. Results of the statistical analysis performed on two-level patients were inconclusive and therefore safety and effectiveness for two-level patients were not established. The BAK/C Interbody Fusion System is not indicated for patients affected with cervical degenerative disc disease at more than one level. ***The results summarized below pertain to one-level patients only.***

(1) Fusion

Fusion: Bayesian Analysis Results

Table 7 provides the Bayesian fusion success results based on the patient population referenced in Table 6**.** The lower and upper limits of the posterior distributions of the difference in BAK/C and ACDF success rates are summarized.

Table 7: Long-term[1] Fusion – Bayesian Analysis Results (Restricted[2] Cohort)

Success Measure	95% Credible Interval for Difference in BAK/C and ACDF Rates[3]	Multivariate Longitudinal Bayesian Analysis Conclusion
Fusion	(+3.2, +6.1)	BAK/C is superior to ACDF

[1] Follow-up examination conducted 24 months post-operatively or later
[2] See *Analysis Cohorts* in Section 11.e. for an explanation of the Restricted and Unrestricted Cohorts
[3] Predictive distributions calculated from Long-Term multivariate longitudinal Bayesian results

Fusion: Classical Analysis Results

Table 8 presents fusion success rates for patients over time. The analysis showed a statistically significant difference in fusion rates between the study groups at the 6-month, 12-month, and long-term follow-up, attributable to lower rates of fusion in the Control group.

Table 8: Long-term[1] Fusion - Classical Analyses Results (Restricted[2] Cohort)

	BAK/C		Control		
	x/n	%	x/n	%	P
6 month	119/120	99.2	77/94	81.9	<0.001
12 month	123/126	97.6	86/97	88.7	0.010
Long-Term	86/86	100.0	66/69	95.7	0.086

[1] Follow-up examination conducted 24 months post-operatively or later
[2] See *Analysis Cohorts* in Section 11.e. for an explanation of the Restricted and Unrestricted Cohorts

(2) Neck Pain

Neck Pain: Bayesian Analysis Results

Table 9 provides the Bayesian neck pain success results based on the patient population referenced in Table 6**.** The lower and upper limits of the posterior distributions of the difference in BAK/C and ACDF success rates are summarized.

Table 9: Long-Term[1] Neck Pain – Bayesian Analysis Results (Restricted[2] Cohort)

Success Measure	95% Credible Interval for Difference in BAK/C and ACDF Rates[3]	Multivariate Longitudinal Bayesian Analysis Conclusion
Neck Pain	(-5.6, +3.7)	Satisfies criterion for equivalence

[1] Follow-up examination conducted 24 months post-operatively or later
[2] See *Analysis Cohorts* in Section 11.e. for an explanation of the Restricted and Unrestricted Cohorts
[3] Predictive distributions calculated from Long-Term multivariate longitudinal Bayesian results

Neck Pain: Classical Analysis Results

Table 10 presents the neck pain success rates for study group at 6, 12, and long-term. No statistical differences in neck pain success were found between the study groups.

Table 10: Long-Term[1] Neck Pain -Classical Analysis Results (Restricted[2] Cohort)

	BAK/C		Control		
	x/n	%	x/n	%	p
6 month	108/135	80.0	76/103	73.8	Not significant
12 month	108/138	78.3	83/100	83.0	Not significant
Long-Term	76/90	84.4	59/71	83.1	Not significant

[1] Follow-up examination conducted 24 months post-operatively or later
[2] See *Analysis Cohorts* in Section 11.e. for an explanation of the Restricted and Unrestricted Cohorts

(3) Overall Radicular

Overall Radicular: Bayesian Analysis Results

Table 11 provides the Bayesian radicular success results based on the patient population referenced in Table 6**.** The lower and upper limits of the posterior distributions of the difference in BAK/C and ACDF success rates are summarized.

Table 11: Long-Term[1] Radicular – Bayesian Analysis Results (Restricted[2] Cohort)

Success Measure	95% Credible Interval for Difference in BAK/C and ACDF Rates[3]	Multivariate Longitudinal Bayesian Analysis Conclusion
Radicular	(-0.7, +9.3)	Satisfies criterion for equivalence

[1] Follow-up examination conducted 24 months post-operatively or later
[2] See *Analysis Cohorts* in Section 11.e. for an explanation of the Restricted and Unrestricted Cohorts
[3] Predictive distributions calculated from Long-Term multivariate longitudinal Bayesian results

Overall Radicular: Classical Analysis Results

Table 12 presents a summary of overall radicular success rates by study group across time. No statistical differences were found between study groups.

Table 12: Long-Term[1] Radicular–Classical Analysis Results (Restricted[2] Cohort)

	BAK/C		Control		
	x/n	%	x/n	%	p
6 month	99/160	61.9	66/130	50.8	Not significant
12 month	104/137	75.9	74/100	74.0	Not significant
Long-Term	72/90	80.0	54/71	76.1	Not significant

[1] Follow-up examination conducted 24 months post-operatively or later
[2] See *Analysis Cohorts* in Section 11.e. for an explanation of the Restricted and Unrestricted Cohorts

(4) Function

Function: Bayesian Analysis Results

Table 13 provides the Bayesian function success results based on the patient population referenced in Table 6**.** The lower and upper limits of the posterior distributions of the difference in BAK/C and ACDF success rates are summarized.

Table 13: Long-Term[1] Function-Bayesian Analysis Results (Restricted[2] Cohort)

Success Measure	95% Credible Interval for Difference in BAK/C and ACDF Rates[3]	Multivariate Longitudinal Bayesian Analysis Conclusion
Function	(-2.1, +7.1)	Satisfies criterion for equivalence

[1] Follow-up examination conducted 24 months post-operatively or later
[2] See *Analysis Cohorts* in Section 11.e. for an explanation of the Restricted and Unrestricted Cohorts
[3] Predictive distributions calculated from Long-Term multivariate longitudinal Bayesian results

Function: Classical Analyses Results

Table 14 presents a summary of function success rates by study group across time. No statistical differences were observed between study groups.

Table 14: Long-Term[1] Function Classical Analyses Results (Restricted[2] Cohort)

	BAK/C		Control		
	x/n	%	x/n	%	p
6 month	107/131	81.7	74/95	77.9	Not significant
12 month	101/136	74.3	80/100	80.0	Not significant
Long-Term	70/89	78.7	51/68	75.0	Not significant

[1] Follow-up examination conducted 24 months post-operatively or later
[2] See *Analysis Cohorts* in Section 11.e. for an explanation of the Restricted and Unrestricted Cohorts

(5) Overall Success

Overall Success: Bayesian Analysis Results

Table 15 provides the Bayesian overall success results based on the patient

population referenced in Table 6**.** The lower and upper limits of the posterior distributions of the difference in BAK/C and ACDF success rates are summarized.

Table 15: Long-Term[1] Overall Success-Bayesian Analysis Results (Restricted[2] Cohort)

Success Measure	95% Credible Interval for Difference in BAK/C and ACDF Rates[3]	Multivariate Longitudinal Bayesian Analysis Conclusion
Overall Success	(+9.9, +19.0)	Satisfies criterion for equivalence

[1] Follow-up examination conducted 24 months post-operatively or later
[2] See *Analysis Cohorts* in Section 11.e. for an explanation of the Restricted and Unrestricted Cohorts
[3] Predictive distributions calculated from Long-Term multivariate longitudinal Bayesian results

Overall Success: Classical Analysis Results

Table 16 presents a summary of Overall Success rates by study group and across time. At the 6-month follow-up, the overall success rate for the Control group was statistically significantly lower than the overall success rate for the BAK/C group. This finding is consistent with the lower rate of fusion success previously reported in the Control group at the 6-month follow-up.

Table 16: Long-Term[1] Overall Success-Classical Analysis Results (Restricted[2] Cohort)

	BAK/C		Control		
	x/n	%	x/n	%	p
6 month	66/114	57.9	32/83	38.6	0.009
12 month	73/124	58.9	53/93	57.0	Not significant
Long-Term	56/85	65.9	35/66	53.0	Not significant

[1] Follow-up examination conducted 24 months post-operatively or later
[2] See *Analysis Cohorts* in Section 11.e. for an explanation of the Restricted and Unrestricted Cohorts

(6) Effectiveness Analysis – Intent-To-Treat

An "intent-to-treat" analysis of efficacy data was also performed. All missing data (other than missing due to patient death) were considered "failures (i.e., included in the denominators of the calculated rates). This categorization of unobserved data results in outcome rates that are lower than the rates reported in the actual observed clinical data. Table 17 presents a summary of the results from the intent-to-treat analyses.

Table 17: Long-Term[1] Effectiveness Analysis –Intent-To-Treat

	BAK/C		Control	
	x/n	%	x/n	%
Fusion				
6 month	119/160	74.4	77/130	59.2
12 month	123/150	82.0	86/122	70.5
Long-Term	86/101	85.1	66/87	75.9
Neck Pain				
6 month	108/160	67.5	76/130	58.5
12 month	108/150	72.0	83/122	68.0
Long-Term	76/101	75.2	59/87	67.8
Radicular				
6 month	99/160	61.9	66/130	50.8
12 month	104/150	69.3	74/122	60.7
Long-Term	72/101	71.3	54/87	62.1
Function				
6 month	107/160	66.9	74/130	56.9
12 month	101/150	67.3	80/122	65.6
Long-Term	70/101	69.3	51/87	58.6
Overall Success				
6 month	66/160	41.3	32/130	24.6
12 month	73/150	48.7	53/122	43.4
Long-Term	56/101	55.4	35//87	40.2

[1] Follow-up examination conducted 24 months post-operatively or later

i. Safety Analyses – Bayesian Analysis Results

Table 18 presents *freedom from complications* results from the multivariate longitudinal Bayesian analysis.

Table 19 presents *freedom from complications requiring additional surgery* results from the multivariate longitudinal Bayesian analysis.

Table 18: All Complications – Bayesian Analysis Results

Success Measure	BAK/C[1]	Control[1]	Bayesian Analysis Conclusion
Freedom from All Complications	85.1	74.7	Satisfies criterion for equivalence

[1] Based on Lifetable Analysis

Table 19: Complications Requiring Additional Surgery – Bayesian Analysis Results

Success Measure	BAK/C[1]	Control[1]	Bayesian Analysis Conclusion
Freedom from Additional Surgery Complications	93.8	89.2	Satisfies criterion for equivalence

[1] Based on Lifetable Analysis

j. Device Failures and Replacements

No device failures were reported during the course of the clinical study. No device replacements were required during the course of the study.

k. Conclusions Drawn from the Studies

Using the "24-month or later" outcome data, effectiveness and safety of BAK/C devices in 1-level patients were established based on equivalence conclusions for all efficacy and safety criteria.

The results of the clinical study provide reasonable assurance that the BAK/C Interbody Fusion System is safe and effective for the indicated patient population.

12. Panel Recommendations

On January 19, 2001, the Orthopedic and Rehabilitation Devices Panel recommended unanimously that this PMA be found approvable with conditions. The conditions were as follows:

a. Limit approval to one-level cases.
b. Require the sponsor to perform a sensitivity analysis to determine effect of high drop-out rate in control group (after randomization, but before implantation).
c. Require the sponsor to conduct a post-approval study to collect 5-year post-operative data where post-approval study employs same outcome assessments as IDE.
d. Require the sponsor to evaluate the HA-coating risk/benefit.
e. Require the sponsor to provide fatigue and static testing of post-sterilized HA-coated version of the device.
f. Require the sponsor to conduct testing on the uncoated devices, or justify why the 6mm device is truly worst case and why simple axial, compressive loading is representative of physiologic loading.

13. CDRH Decision

CDRH concurred with the Panel's recommendation of January 19, 2001, and issued a letter to Sulzer Spine-Tech on March 2, 2001, advising that its PMA was approvable subject to the following conditions as recommended by the Panel and required by FDA:

a. Modify the device labeling and Summary of Safety and Effectiveness Data to limit approval to one-level cases.
b. Conduct an additional sensitivity analysis to determine the effect of the high drop-out rate in the control group after randomization, but before implantation.
c. Conduct a post-approval study to assess the long-term (5 years post-operative) performance of the BAK/C.
d. Develop an additional post-approval study that focuses on retrieval assessment of any BAK/C that is implanted and subsequently removed.
e. Develop a surgeon training program and describe the methods which assure than surgeons can receive this training prior to implanting the device in patients.

In an amendment received by FDA on April 6, 2001, Sulzer Spine-Tech submitted the required data. The information provided by Sulzer Spine-Tech satisfactorily addressed the above conditions of approval. After receipt of this amendment, FDA continued to work with the sponsor to finalize product labeling. FDA issued an approval order on April 20, 2001.

Inspections of the sponsor's manufacturing facilities and sterilization sites were completed prior to April 20, 2001. The sites were found to be in compliance with the device Good Manufacturing Practice regulations.

The PMA for the BAK/C was granted expedited review status on January 29, 1999, because the device potentially represented a clinically meaningful advantage over existing technology. By eliminating the need to harvest bone from a second surgical site (e.g., iliac crest), the BAK/C eliminates the morbidity associated with such harvesting. In addition, use of autograft bone in a cervical fusion procedure has been shown to have several advantages over allograft bone (e.g., lower rate of graft collapse and higher rate of fusion).

14. Approval Specifications

Directions for Use: See product labeling.

Hazard to Health from Use of the Device: See Indications, Contraindications, Warnings, and Precautions, and Adverse Reactions in the labeling.

Post Approval Requirements and Restrictions: See the Approval Order.