P970015

SUMMARY OF SAFETY AND EFFECTIVENESS

I. GENERAL INFORMATION

DEVICE GENERIC NAME:	Intervertebral Body Fusion Device
DEVICE TRADE NAME:	INTER FIX™ Threaded Fusion Device
APPLICANT'S NAME:	Sofamor Danek USA 1800 Pyramid Place Memphis, TN 38132
PREMARKET APPROVAL (PMA) APPLICATION NUMBER:	P970015
DATE OF PANEL RECOMMENDATION:	December 11, 1997
DATE OF NOTICE OF APPROVAL TO THE APPLICANT:	May 14, 1999

II. INDICATIONS FOR USE

The INTER FIX™ Threaded Fusion Device is indicated for spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at one level from L2-S1. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history and radiographic studies. These DDD patients may also have up to Grade I spondylolisthesis or retrolisthesis at the involved level. INTER FIX™ implants are to be used with autogenous bone graft and implanted via an open anterior approach.

III. DEVICE DESCRIPTION

The INTER FIX™ Threaded Fusion Device is comprised of a hollow, threaded cylinder and a removable endcap. The cylinders are available in 18 sizes. The diameters range from 12mm to 20mm and the lengths range from 20mm to 29mm. The endcap component is available in corresponding diameters, ranging from 12mm to 20mm. Each cylinder component has a 30° included angle V-thread over the entire outer surface of the implant and a 45° chamfer at the ends. Each cylinder component has multiple through-holes that are placed cephalad and caudad and multiple small transverse holes intended to allow for bony ingrowth. The INTER FIX™ Threaded Fusion Device is manufactured from titanium alloy (Ti-6Al-4V) which conforms to American Society Testing and Materials (ASTM) Standard F136.

9

IV. CONTRAINDICATIONS

The INTER FIX™ Threaded Fusion Device should not be implanted in patients with an active infection at the operative site or with an allergy to titanium or titanium alloy.

V. WARNINGS

- The INTER FIX™ Threaded Fusion Device should only be used by surgeons who are experienced in spinal fusion procedures and have undergone adequate training with this device.

- A lack of adequate experience and/or training may lead to a higher incidence of adverse events such as vascular injuries, neurological events, and/or urogenital events (including retrograde ejaculation).

VI. PRECAUTIONS

- The safety and effectiveness of the INTER FIX™ Threaded Fusion Device have not been established in patients with any of the following conditions:
  - spondylolisthesis or retrolisthesis of Grade II or greater;
  - more than one level to be fused;
  - revision of previous interbody fusion procedure(s);
  - postoperative steroidal or nonsteroidal anti-inflammatory medication requirements;
  - gross obesity;
  - ages less than 18 years or greater than 65 years;
  - osteoporosis, osteopenia, and/or osteomalacia;
  - pregnancy.

- The safety and effectiveness of the INTER FIX™ Threaded Fusion Device have only been established in anterior lumbar interbody fusion (ALIF) procedures using autologous bone graft.

- Patients receiving the INTER FIX™ Threaded Fusion Device should have had at least six months of nonoperative treatment.

- Two INTER FIX™ Threaded Fusion Devices should be implanted side by side at the surgical level.

10

- The long axis of the INTER FIX™ Threaded Fusion Devices should be in the anterior-posterior direction.

- The implants and instruments must be sterilized prior to use according to the sterilization instructions as provided in the package insert, unless supplied sterile and clearly labeled as such.

VII. ADVERSE EFFECTS

From the multicenter clinical trial, a total of 181 patients receiving the INTER FIX™ device and 62 control patients were evaluated for adverse events. The control patients received surgical treatment using a femoral ring allograft filled with iliac crest-derived autogenous bone.

Adverse events occurring in clinical trial patients are presented in Table I. The rates presented are the number of occurrences for a particular adverse effect divided by the total number of patients with available data at a given time period. The adverse events occurring in the randomized and nonrandomized INTER FIX™ device treatment groups are combined in order to present an overall rate.

Table I - Adverse Effects[1]

Complication	Operative (Number (%))		Post-operative (1 Day-<2 Months) (Number (%))		3 Month (≥2-<6 Months) (Number (%))		6 Month (≥6-<9 Months) (Number (%))		12 Month (≥9-<19 Months) (Number (%))		24 Month (≥19-< 30 Months) (Number (%))		ADVERSE EVENTS	
	INTER FIX™ N=181	Control N=62	INTER FIX™ N=179	Control N=62	INTER FIX™ N=172	Control N=60	INTER FIX™ N=153	Control N=59	INTER FIX™ N=133	Control N=54	INTER FIX™ N=72	Control N=48	INTER FIX™ # (% of 181)	Control # (% of 62)
Vascular Intra-Op	15 (8.3)			2 (3.2)									15 (8.3)	2 (3.2)
Sacroiliac Pain			4 (2.2)		3 (1.7)		3 (2.0)	1 (1.7)	4 (3.0)	1 (1.9)	1 (1.4)		15 (8.3)	2 (3.2)
Neurological	3 (1.7)		3 (1.7)	2 (3.2)	4 (2.3)	2 (3.3)	1 (0.7)	1 (1.7)	1 (0.8)	2 (3.7)	1 (1.4)	3 (6.3)	13 (7.2)	10 (16.1)*
Back Pain			1 (0.6)		3 (1.7)	2 (3.3)	5 (3.3)	1 (1.7)	2 (1.5)	3 (5.6)		6 (12.5)	11 (6.1)	12 (19.4)*
Incisional			7 (3.9)	6 (9.7)	1 (0.6)			1 (1.7)	1 (0.8)				9 (5.0)	7 (11.3)
Spinal Event	1 (0.6)		1 (0.6)	1 (1.6)	1 (0.6)		1 (0.7)	1 (1.7)	3 (2.3)		2 (2.8)		9 (5.0)	2 (3.2)
Urological	1 (0.6)		6 (3.4)	2 (3.2)	1 (0.6)								8 (4.4)	2 (3.2)
Other	2 (1.1)			2 (3.2)	2 (1.2)		3 (2.0)		1 (0.8)				8 (4.4)	2 (3.2)
Other Pain			3 (1.7)	1 (1.6)	3 (1.7)			2 (3.4)	1 (0.8)			1 (2.1)	7 (3.9)	4 (6.5)
Gastrointestinal			5 (2.8)	3 (4.8)				1 (1.7)	1 (0.8)			1 (2.1)	6 (3.3)	5 (8.1)
Retrograde Ejaculation			2 (1.1)		3 (1.7)		1 (0.7)						6 (3.3) (7.4)[2]	
Respiratory			3 (1.7)	1 (1.6)	1 (0.6)		1 (0.7)						5 (2.8)	1 (1.6)
Leg Pain			1 (0.6)		1 (0.6)		1 (0.7)		1 (0.8)				4 (2.2)	
Trauma					3 (1.7)				1 (0.8)				4 (2.2)	
Peritoneal	3 (1.7)												3 (1.7)	
Vascular Post-Op			2 (1.1)	2 (3.2)									2 (1.1)	2 (3.2)
Bone Fracture	1 (0.6)		1 (0.6)										2 (1.1)	
Implant Displacement/ Loosening	1 (0.6)	1 (1.6)		5 (8.1)			1 (0.7)						2 (1.1)	6 (9.7)*
Graft Site Pain			1 (0.6)							1 (1.9)			1 (0.6)	1 (1.6)
Non-Union							1 (0.7)						1 (0.6)	
Subsidence							1 (0.7)						1 (0.6)	
Non-Union (OUTCOME PENDING)								1 (1.7)	1 (0.8)			1 (2.1)	1 (0.6)	2 (3.2)
Meningitis						1 (1.7)								1 (1.6)
Implant Breakage		4 (6.5)												4 (6.5)*
Death										1 (1.9)				1 (1.6)

*p < 0.05

The most common and serious adverse events were intraoperative vascular and neurological injuries. A total of 15 vascular intraoperative events occurred in 14 patients in the INTER FIX™ device group. These events included: 2 injuries to the vena cava; 9 injuries to the iliac vein; 1 lacerated hypogastric vein; 1 segmental vein bleeder; 1 sacral vein injury; and 1 superficial bleeder. A total of 2 vascular intraoperative injuries occurred in 2 patients in the control group. These included: 1 injury to an iliac vein and 1 bleeding from the bone bed.

A total of 13 neurological events occurred in 13 patients in the INTER FIX™ device group. These events included: 1 footdrop; 2 nerve root injuries; 1 foraminal stenosis; 1 reflex sympathetic dystrophy; 3 numbness or burning of legs; 2 dysthesia; 2 paresthesia; and 1 shooting pain in lower back. A total of 10 neurological events occurred in 8 patients in the control group. These events included: 1 radiculopathy with tingling extremities; 1 chronic back pain with radiculitis; 1 debilitating distribution symptoms; 2 back and leg pain with

[1] Since fusion is a primary effectiveness endpoint, nonunions reported as adverse events by the investigator are not included in the table if the nonunion resulted in a second surgery. These nonunion events are captured in the secondary surgery table and the fusion table.

[2] Percent of 81 male patients.

12

other symptoms; 1 denervated abductor magnus muscle; and 4 with numbness or warmth in legs. In addition, the adverse effects table presents leg and back pain adverse events and/or spinal events, such as disc space collapse, that, in some instances, had a neurological component. Some of the adverse effects led to surgical interventions subsequent to the clinical trial surgery. These additional surgical interventions can be classified as revisions, removals, supplemental fixations, and reoperations. A revision is a procedure that adjusts or in any way modifies the original implant configuration. A removal is a procedure that removes one or more components of the original implant configuration without replacement with the same type of trial device. Supplemental fixation is a procedure in which additional spinal devices not approved as part of the protocol are placed. A reoperation is any surgical procedure that does not remove, modify or add any original implant components. Table II summarizes the secondary surgical interventions in the INTER FIX™ device (randomized and nonrandomized combined) and control treatment groups.

Table II Secondary Surgical Procedures

	INTER FIX™ Device (N=181)	Control (N=62)
Revisions	4 (2.2%)	3 (4.8%)
Removals	2 (1.1%)	0 (0.0%)
Supplemental Fixations	7 (3.9%)	11 (17.7%)*
Reoperations	11 (6.1%)	6 (9.7%)

*$p < 0.05$

The following is a list of potential adverse effects which may occur with spinal fusion surgery with the INTER FIX™ Threaded Fusion Device. Some of these adverse effects may have been previously reported in the adverse effects table.

- 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.
- Urological system compromise.

- 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.
- Reproductive system compromise.
- 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 correct some of these potential adverse events.

VIII. ALTERNATIVE PRACTICES AND PROCEDURES

Nonoperative alternative treatments may include physical therapy, medications, braces, chiropractic care, bed rest, spinal injections, or exercise programs. In addition, there are alternative spinal fusion techniques. These include posterior lumbar interbody fusion (PLIF) procedures with or without instrumentation, anterior lumbar interbody fusion (ALIF) procedures with or without instrumentation, combined anterior and posterolateral (360°) fusion procedures, anterior/ anterolateral spinal systems (e.g., plate and screw systems), or posterior spinal systems (e.g., pedicle screw/rod and hook/rod systems).

IX. MARKETING HISTORY

In the United States, the INTER FIX™ Threaded Fusion Device manufactured by Sofamor Danek has only been used in IDE studies. Since 1995, the INTER FIX™ Threaded Fusion Device, which has been distributed by Sofamor Danek Europe, has been

marketed in at least 20 countries. It has not been withdrawn from marketing for any reason.

X. SUMMARY OF LABORATORY (MECHANICAL) STUDIES

A Failure Mode and Effects Analysis (FEMA) was conducted on the INTER FIX™ design to determine potential failure modes and their associated causes. Based on the potential failure modes, the following tests were conducted to validate the design of the implant:

- Static Compression Testing
- Cyclic Fatigue Testing
- Stiffness Testing
- Insertion Torque/Push-Out Testing

A. Laboratory Testing

Nonclinical tests were conducted to characterize the mechanical properties of the INTER FIX™ Threaded Fusion Device. The size of the implant used in the studies was 20mm x 29mm which represented the "worst case" scenario (representing the maximum bending stress condition based on mathematical calculations) of the available implant sizes. The endcaps were in place for these tests.

1. Static Compression Testing

Two static compression tests were performed. Five (5) INTER FIX™ implants were tested. The load cell limit was 22,000 N (4946 lbs.). None of the five (5) implants were crushed or exhibited any cracking under microscopic examination following the testing.

Five (5) INTER FIX™ implants also were loaded statically in compression until implant breakage was reached. The mean load to breakage of the five samples tested was 79,797 N (17,939 lbs.). All implants broke by buckling under the load.

The implant's compressive strength exceeds the compressive failure values for a spinal motion segment of between 4000 N – 13000 N.

2. Cyclic Fatigue Testing

Five (5) INTER FIX™ implants were loaded cyclically in compression at loads ranging from 880 N (198 lbs.) to 9600 N (2157 lbs.) at 15 Hz. None of the five (5) implants failed after 5 million cycles. It has been estimated that the number of spinal loading cycles over a 40 years period to be 85 million cycles or

approximately 2.125 million cycles per year thus five million cycles would represent the number of loading cycles a device might experience within two years.

A special flexion-extension or multi-axial cyclic test fixture was developed. The runout value, (i.e., the maximum load at which breakage did not occur at 5,000,000 cycles) for the implant was determined to be approximately 1500 N which translates to a bending moment of 135 N-m. The literature reports that the whole motion segment (i.e., two vertebral bodies separated by a disc) can resist a bending moment of about 33 N-m before it sustains damage.

B. Stability Testing

Two studies were performed to evaluate the stability of the spine following device implantation. The first study examined the effects of implanting the INTER FIX™ Threaded Fusion Device on spinal stiffness. The second study assessed the implant insertion torque and push-out properties.

1. Stiffness Testing

Biomechanical stability testing was performed using lumbar calf spines of similar size and age. A 14mm diameter implant was selected based on anatomical considerations of the calf spines and for comparability to stiffness test results for another interbody fusion device. Stiffness was evaluated in tension, axial torsion, axial loading, and lateral bending using the intact spine as a baseline. These implants were implanted at L3-L4; non-destructive testing was performed at this level.

The results of this study are presented in Table III. The values represent the means of the six implants tested.

Table III Stiffness Testing

	INTER FIX™ Device (N-m/deg)	Normal Spine (N-m/deg)	INTER FIX™ Device/ Normal Ratio
Flexion/Extension	2.15	0.77	3.2
Axial Torsion	1.20	1.37	0.9
Axial Compression	118.41	72.02	1.7
Lateral Bending	2.14	0.51	4.2

These results indicate that the INTER FIX™ Threaded Fusion Device when implanted in a calf spine motion segment increases the stiffness of the motion segment compared to an intact, normal calf spine.

16

2. Insertion Torque and Push-out Testing

Insertion torque and push-out testing was performed using human cadaveric spines. An INTER FIX™ device (16mm diameter) was implanted at the L3-L4 and the L4-L5 disc levels through an anterior lumbar interbody fusion technique. The 16mm diameter implant was selected for testing based on anatomical considerations of the cadaveric spines and for comparability of results to another interbody fusion device. Six INTER FIX™ devices were used in the study. The insertion torque was measured with a special driver which was connected to strain gauges. The insertion torques for the INTER FIX™ device were 0.87 N-m. Push-out values for the implanted devices were determined using a servohydraulic machine. The mean push-out values for the INTER FIX™ device 697 N. No catastrophic push-outs occurred and all implants pushed out via bony failure surrounding the implant.

XI. SUMMARY OF ANIMAL STUDIES

An animal study involving the implantation of a single lateral INTER FIX™ device in the lumbar spines of 20 sheep was performed. The sheep underwent anterior lumbar interbody fusion procedures with either the INTER FIX™ device filled with autogenous iliac crest bone (n=8), autogenous iliac crest dowel grafts (n=6), or interbody decortication only (sham, n=6). Two sheep had malpositioned devices and were excluded. The sheep were sacrificed at 6 months following implantation. Spinal fusion in the sheep was evaluated following sacrifice by manual palpation and histologically. The sheep were radiographed immediately after surgery and at 2, 4,and 6 months after surgery. Interbody distraction and angulation were measured at each time point. The stiffness to flexion, extension, and lateral bending moments of the spine were also measured. Twelve untreated cadaveric spines were also tested for comparison.

All of the sheep (100%) were found to be fused at the operated levels upon manual palpation. Histological evaluation yielded a 37% rate of complete bony bridging. For cases where fusion was noted, there was bone in contact with the outer surfaces of the devices and, in many cases, distinct anterior bony bridging. The autograft bone in the device did not appear to be undergoing resorption by osteoclasts.

Interbody distraction successfully occurred in INTER FIX™ device sites and autograft-implanted sites. During the first two months following surgery, loss of postoperative interbody height occurred in all groups. Percentage loss of height was lowest in the INTER FIX™ device sites (INTER FIX™ device = 21.0%, autograft dowels = 59.3%, sham = 88.8%). By six months following surgery, only the INTER FIX™ device sites remained distracted beyond the normal spine in terms of disc/vertebrae ratio. Stiffness results are presented in Table IV.

17

Table IV - Stiffness Results				
	INTER FIX™ Device (N-m/deg)	**Autograft Dowel (N-m/deg)**	**Sham (N-m/deg)**	**Untreated (N-m/deg)**
Flexion	10.58	16.34	26.24	5.98
Extension	24.34	27.71	31.85	5.46
Right Bending	14.79	26.99	26.23	2.67
Left Bending	19.84	33.50	33.34	3.55

Fusions in all groups were statistically significantly stiffer than untreated spines ($p < 0.05$). Autograft sites were statistically significantly stiffer than INTER FIX™ device sites in lateral bending (right bending, $p = 0.020$ and left bending, $p = 0.040$). Sham sites were stiffer than INTER FIX™ device and autograft sites to flexion ($p = 0.002$ and $p=0.040$, respectively), but this likely resulted from complete intervertebral collapse.

XII. BIOCOMPATABILITY

The INTER FIX™ Threaded Fusion Device is fabricated from medical grade titanium alloy comforming to American Society Testing and Materials (ASTM) Standard F136. Titanium alloy has a long history of use in orthopedic devices, including spinal implants, and has a well-established biocompatability profile.

XIII. SUMMARY OF CLINICAL INVESTIGATION

A clinical trial of the INTER FIX™ Threaded Fusion Device was conducted in the United States in accordance with approved IDE.

A. Objective

A multi-center clinical trial of the INTER FIX™ Threaded Fusion Device was conducted in the United States to determine the safety and effectiveness of the anterior spinal use of the INTER FIX™ device in the treatment of patients with symptomatic degenerative disc disease. Investigational patients were treated with the INTER FIX™ device filled with autogenous bone derived from the iliac crest. Control patients were treated with femoral ring allograft also filled with iliac crest-derived autogenous bone.

B. Inclusion and Exclusion Criteria

Patients admitted to the clinical trial had symptomatic degenerative disc disease as noted by intractable leg and/or back pain with positive diagnostic imaging finding(s).

In addition, patients had to exhibit spinal instability as defined by greater than 4 mm of translation or greater than 5° of angulation on flexion/extension radiographs, have single level symptomatic involvement from L2-S1, and have no greater than Grade 1 spondylolisthesis. Specifically excluded from the clinical trial were patients who: had a previous anterior interbody fusion procedure at the involved spinal level; had osteopenia, osteoporosis, or osteomalacia; or required bone growth stimulation.

C. Clinical Trial Design

Initially, the clinical trial had a prospective, randomized, controlled design. Subsequently, the investigational plan was revised to allow patients to be entered into a non-randomized arm, i.e., patients treated with INTER FIX™ device only. The study was approved for 20 sites and 350 symptomatic degenerative disc disease (DDD) subjects (60-70 randomized investigational patients, 50-55 randomized control patients, and 230-240 nonrandomized investigational patients). The entire clinical trial was designed to demonstrate equivalence between the INTER FIX™ device and control treatments at the 24 month time point. Study success was based on a comparison of the rate of successful patient outcomes in the treatment and control groups.

D. Patient Population and Demographics

A total of 181 patients were entered in the INTER FIX™ device arm of the clinical trial. Seventy-seven (77) patients were in the randomized INTER FIX™ device treatment arm and 104 patients were in the nonrandomized arm. The nonrandomized arm included 3 patients who did not receive the INTER FIX™ device treatment due to surgical adverse events. A total of 62 control patients were entered into the clinical trial. All control patients were part of the randomized treatment arm.

Demographic information pertaining to the patients participating in the clinical trial is presented in Table V. The demographic characteristics of all treatment groups were similar.

Table V - Demographic Information			
	INTER FIX™ Device (Randomized)	INTER FIX™ Device (Nonrandomized)	Control
Age (yr.) Mean [Range]	N = 77 41.0 [18-64]	N = 104 41.1 [23–62]	N = 62 41.2 [27-59]
Weight (lbs.) Mean [Range]	N = 77 170.5 [100-270]	N = 102 171.7 [102-254]	N = 62 172.8 [109-250]
Height (in.) Mean [Range]	N = 76 66.6 [60-75]	N = 102 67.5 [57-78]	N = 62 67.9 [60-74]
Sex - Freq. (%) Male Female	 30 (39.0%) 47 (61.0%)	 51 (49.0%) 53 (51.0%)	 33 (53.2%) 29 (46.8%)
Tobacco used - Freq. (%) Yes No	 23 (29.9%) 54 (70.1%)	 25 (24.3%) 78 (75.7%)	 20 (32.3%) 42 (67.7%)
Workers Comp. - Freq. (%) Yes No	 32 (42.1%) 44 (57.9%)	 29 (28.2%) 74 (71.8%)	 22 (35.5%) 40 (64.5%)
Taking Preop. Medication for Pain - Freq. (%) Yes No	 59 (76.6%) 18 (23.4%)	 81 (78.6%) 22 (21.4%)	 46 (74.2%) 16 (25.8%)
Previous Back Surgery -Freq. (%) Yes No	 32 (41.6%) 45 (58.4%)	 38 (37.7%) 64 (62.8%)	 27 (43.6%) 35 (56.5%)

E. Evaluation Schedule

Patients were evaluated preoperatively, perioperatively, and postoperatively at 3, 6, 12, and 24 months following surgery.

F. Patient Accountability

The database was closed for analysis as of January 12, 1999. The number of INTER FIX™ device and control patients evaluated at each time point are summarized in Table VI. In the randomized treatment arm, there are only three INTER FIX™ device patients and one control patient who have not reached their 2 year postoperative anniversary and who have not been evaluated. For the nonrandomized INTER FIX™ device treatment arm, 82 patients have reached their one year anniversary, and 6 patients have reached their two year postoperative anniversary.

Table VI - Number of Patients Evaluated at each Timepoint						
Treatment Group	Preoperative	Surgery/ Discharge	3 Months	6 Months	12 Months	24 Months
INTER FIX™ Device (Randomized)	77	76	75	74	68	67
INTER FIX™ Device (Nonrandomized)	104	104	97	80	65	5
Control	62	62	60	59	54	48

G. Effectiveness Analyses

The effectiveness variables included assessment of fusion at the involved level, pain/disability status, neurological status, general health status, disc height status, and overall success. In some cases, only partial data were available (i.e., not all of the outcome measures were obtained for all patients at all follow-up points). In these cases, all available outcomes were summarized in the analyses. Therefore, the number of patients included in the assessment of the outcomes varies slightly due to missing data. The effectiveness analyses involved the comparison of the randomized INTER FIX™ device group to the control group. Clinical results from the nonrandomized INTER FIX™ device group are also presented for comparative purposes.

1. Effectiveness Analysis—Fusion

Fusion of the surgically treated vertebral bodies was determined using A/P, lateral, and flexion/extension radiographs. The radiographs were interpreted by an independent, board certified radiologist. The radiologist assessed the fusion status of study patients at 6, 12, and 24 months following surgery. To be considered fused, there had to be evidence of bridging trabecular bone, translational stability (≤ 3mm) and angular motion stability (<5°), and the absence of radiolucent lines around more than 50% of the implant(s). Also, patients having secondary surgeries due to nonunions were considered as having failed fusions and were included in the fusion calculations. Fusion rates were based on patients with available data for both INTER FIX™ device arms and the control group and are provided in Table VII.

Table VII - Fusion Rates (%) at 6, 12, and 24 Months			
Treatment Group	6 Month Rate	12 Month Rate	24 Month Rate
INTER FIX™ Device (Randomized)	95.0 (38/40)	96.7 (58/60)	96.9 (63/65)
INTER FIX™ Device (Nonrandomized)	93.6 (29/31)	96.1 (49/51)	100.0 (3/3)
Control	18.8 (6/32)	48.8 (21/43)	56.3 (27/48)

2. Effectiveness Analysis—Pain/Disability

The Oswestry Low Back Pain Disability Questionnaire was used to measure how back pain affected the patient's ability to manage in everyday life (i.e., a combined measure of pain and disability). The Oswestry Questionnaire is based on a patient's response to ten questions which focus on pain, personal care, lifting, walking, sitting, standing, sleeping, sex life, social life, and ability to travel. The responses to each question range from zero to five. A lower numeric score represented a better pain and disability status regarding that variable. A total Oswestry score can be determined by summing the scores of the individual questions and dividing that total by the maximum possible total score (50 if all questions are answered). This yields a percentage. Therefore, Oswestry scores are in a range of 0% to 100%, with a lower percentage indicating less pain and disability. The Oswestry Questionnaire was administered preoperatively as well as at each postoperative visit.

The mean composite Oswestry scores for INTER FIX™ patients with available data for the different study periods are provided in Table VIII.

Table VIII Mean Oswestry Pain/Disability Scores

Treatment Group	Preoperative	6 Months	12 Months	24 Months
INTER FIX™ Device (Randomized)	51.1 (N=77)	33.7 (N=73)	32.9 (N=66)	29.4 (N=67)
INTER FIX™ Device (Nonrandomized)	48.1 (N=103)	31.9 (N=74)	29.6 (N=59)	18.5 (N=4)
Control	52.7 (N=60)	38.4 (N=57)	35.0 (N=54)	31.5 (N=48)

Based on patients with available data, Table IX shows the distribution of patients demonstrating various levels of preoperative to postoperative improvement in Oswestry scores.

Table IX: Pain Improvement Rates (%) at 6, 12 and 24 Months									
	6 Month Rates			12 Month Rates			24 Month Rates		
Preoperative to Postoperative Improvement	INTER FIX™ Device		Control	INTER FIX™ Device		Control	INTER FIX™ Device		Control
	Rand.	Nonrand		Rand.	Nonrand		Rand.	Nonrand	
1 Point	87.7 (64/73)	82.4 (61/74)	72.7 (40/55)	86.4 (57/66)	84.7 (50/59)	75.5 (40/53)	91.0 (61/67)	75.0 (3/4)	82.6 (38/46)
5 Points	78.1 (57/73)	71.6 (53/74)	65.5 (36/55)	77.3 (51/66)	79.7 (47/59)	71.7 (38/53)	80.6 (54/67)	75.0 (3/4)	71.7 (33/46)
10 Points	65.8 (48/73)	62.2 (46/74)	52.7 (29/55)	69.7 (46/66)	67.8 (40/59)	64.2 (34/53)	74.6 (50/67)	75.0 (3/4)	69.6 (32/46)
15 Points	54.8 (40/73)	50.0 (37/74)	40.0 (22/55)	51.5 (34/66)	55.9 (33/59)	50.9 (27/53)	59.7 (40/67)	75.0 (3/4)	52.2 (24/46)

3. Effectiveness Analysis—Neurological

The neurological status of the patients participating in the clinical trial was assessed preoperatively and postoperatively at every follow-up visit. The neurological status assessment tool addressed motor function, sensory, reflexes, and the degree of straight leg raise reproducing leg pain. An algorithm was developed to transform the detailed scores for each parameter into an overall classification representing a maintenance or improvement in neurological status at a given postoperative time as compared to their preoperative neurological status. Overall neurological status maintenance or improvement is based on demonstrating maintenance or improvement in at least three of the four categories. Table X shows the distributions of patients with available data in the treatment groups having a maintenance or improvement in condition following surgery for the various neurological parameters.

23

Table X Neurological Maintenance or Improvement Rates (%) at 6, 12, and 24 Months					
Treatment Group	**Motor Function**	**Sensory**	**Reflexes**	**SLR**	**Overall**
6 Months					
INTER FIX™ Device (Randomized)	100.0 (72/72)	95.8 (69/72)	88.9 (64/72)	96.7 (59/61)	97.2 (70/72)
INTER FIX™ Device (Nonrandomized)	100.0 (75/75)	96.0 (72/75)	94.7 (71/75)	100.0 (75/75)	98.7 (74/75)
Control	100.0 (56/56)	100.0 (56/56)	94.6 (53/56)	97.9 (47/48)	98.2 (55/56)
12 Months					
INTER FIX™ Device (Randomized)	100.0 (66/66)	98.5 (65/66)	93.9 (62/66)	96.3 (52/54)	100.0 (66/66)
INTER FIX™ Device (Nonrandomized)	96.7 (58/60)	95.0 (57/60)	90.0 (54/60)	98.3 (59/60)	98.3 (59/60)
Control	100.0 (52/52)	98.1 (52/53)	94.3 (50/53)	97.9 (47/48)	98.1 (52/53)
24 Months					
INTER FIX™ Device (Randomized)	100.0 (66/66)	98.5 (65/66)	87.9 (58/66)	90.9 (60/66)	95.5 (63/66)
INTER FIX™ Device (Nonrandomized)	100.0 (4/4)	100.0 (4/4)	100.0 (4/4)	100.0 (4/4)	100.0 (4/4)
Control	97.7 (42/43)	93.0 (40/43)	97.7 (42/43)	90.7 (39/43)	97.7 (42/43)

4. Effectiveness Analysis—General Health

The Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) was used to assess general health status of all study patients. The SF-36 is a self-administered test to be completed by the patient prior to surgery and at each post-operative visit. The SF-36 scale measures specific health concepts related to physical functioning and limitations, social functioning, as well as health perceptions. The questionnaire contains 36 questions which pertain to eight subscales of health status. These eight subscales are physical function, role-physical, pain index, general health perception, vitality, social function, role emotional, and mental health.

These eight SF-36 scales can be summarized into two measures pertaining to physical health and mental health. The physical health summary (PCS) is based primarily on the physical functioning, role-physical, bodily pain, and general health scales of the SF-36 survey. The mental health summary (MCS) is comprised primarily of the vitality, social functioning, role-emotional, and mental health scales. Table XI presents the mean PCS and MCS results for patients with available data in the two treatment groups at various study periods. Higher numbers represent increasing improvement in general health.

24

Table XI Mean PCS and MCS Scores at 6, 12, and 24 Months								
	Preoperative		6 Month		12 Month		24 Month	
Treatment Group	PCS	MCS	PCS	MCS	PCS	MCS	PCS	MCS
INTER FIX™ Device (Randomized)	28.3 N=77	42.2 N=77	35.3 N=71	46.5 N=71	37.9 N=66	46.3 N=66	39.9 N=66	46.7 N=66
INTER FIX™ Device (Nonrandomized)	28.3 N=103	43.1 N=103	36.1 N=75	48.8 N=75	37.9 N=59	50.2 N=59	47.6 N=4	47.9 N=4
Control	28.5 N=61	41.9 N=61	36.4 N=55	47.1 N=55	36.8 N=54	46.5 N=54	37.3 N=48	51.1 N=48

All of the mean postoperative scores were higher than preoperative scores for the treatment groups.

5. **Effectiveness Analysis—Disc Height**

In addition to the clinical results presented above, disc height measurements were made from the radiographs. The disc height was considered to be maintained or improved if either the anterior or posterior postoperative disc height was no more than 2mm less than the preoperative height. . Based on patients with available data, the rates of disc height maintenance or improvement at 12 and 24 months following surgery are presented in Table XII.

Table XII Disc Height Maintenance or Improvement Rates (%) at 6, 12, and 24 Months			
Treatment Group	6 Month Rate	12 Month Rate	24 Month Rate
INTER FIX™ Device (Randomized)	100.0 (65/65)	96.7 (58/60)	98.4 (60/61)
INTER FIX™ Device (Nonrandomized)	100.0 (24/24)	97.4 (37/38)	100.0 (3/3)
Control	95.7 45/47	97.9 (47/48)	97.5 (39/40)

6. **Effectiveness Analysis—Overall Success**

Study success was based on a comparison of the rate of successful patient outcomes in the treatment and control groups. A successful outcome for an individual patient was based on the following endpoints: a patient demonstrating fusion (as previously defined above); 15 point improvement in Oswestry scores; and neurological status maintenance or improvement (no worse in MCS and PCS scores). General health status and disc height results were not included in the overall success calculations. Table XIII provides this information based on patients with available data for the randomized INTER FIX™ device results.

Table XIII - Overall Success Rates (%) from Randomized Arm at 12 and 24 Months					
	12 Month Rates		24 Month Rates		
	INTER FIX™ Device	Control	INTER FIX™ Device	Control	Delta (Δ)
Overall Success	49.1 (28/57) [N=74]	31.6 (12/38) [N=56]	59.7 (37/62) [N=67]	48.6 (17/35) [N=48]	0.07
Overall Success Accounting for Second Surgery Failures*	46.7 (28/60) [N=77]	28.6 (12/42) [N=60]	55.2 (37/67) [N=72]	37.8 (17/45) [N=58]	0.01

*Note, second surgery failures consists of patients who received a second surgery due to being a failure. Second surgery failures were omitted from all follow-up time points subsequent of being determined a failure.

Statistical comparisons of the overall success rates at 24 months showed the randomized INTER FIX™ device results were statistically no worse than the control group results using a delta of 0.20 as per the approved IDE. Because CDRH had a concern that a delta of 0.20 may not be clinically significant, a retrospective analysis was conducted and based on the observed overall success rates, the randomized INTER FIX™ device results were statistically no worse than the control group results by a delta of 0.07 and 0.01 accounting for second surgery failures.

Table XIV presents the 12 and 24 month clinical trial results for patients with available data treated with the INTER FIX™ Threaded Fusion Device in the nonrandomized arm of the clinical trial.

Table XIV - Overall Success Rates (%) from Nonrandomized Arm at 12 and 24 Months		
	INTER FIX™ Device	
	12 Month Rates	24 Month Rates
Overall Success	57.8 (26/45) [N=74]	66.7 (2/3) [N=6]
Overall Success Accounting for Second Surgery Failures	53.1 (26/49) [N=80]	66.7 (2/3) [N=6]

7. Effectiveness Analysis—Intent-To-Treat

An "intent-to-treat" analysis of the randomized INTER FIX™ group was also performed. For this analysis, secondary surgery failures, deaths, patients lost-to-follow-up, and missing observations due to other causes resulted in missing observations for the outcome variables and therefore were included in the

denominators of the calculated rates, i.e., considered as "failures". By treating these unobserved data as treatment failures, the clinical outcome rates in the intent-to-treat analysis naturally will be lower than the rates reported in the actual observed clinical data. Table XV provides the results for the intent-to-treat analysis.

Table XV Intent-to-Treat Analysis for INTER FIX™ Device
Deaths, Secondary Surgery Failures, Lost-to-Follow-up, and Missing Observations Are Considered as Failures and Are Included in the Denominator of the Rates

	12 Month Rates Randomized	12 Month Rates Randomized and Nonrandomized	24 Month Rates Randomized
Fusion	75.3% (58/77)	67.3% (107/159)	85.1% (63/74)
Oswestry Pain/Disability Improvement Patients with at least 15 Point Improvement from Pre-Op	44.2% (34/77)	42.1% (67/159)	54.1% (40/74)
Neurological Status Maintenance or Improvement	85.7% (66/77)	78.6% (125/159)	85.1% (63/74)
Overall Success	36.4% (28/77)	34.0% (54/159)	50.0% (37/74)
Secondary Surgery Failures			
Nonunions[3]	2	2	2
Other[4]	1	8[5]	3
Deaths	0	0	0

[3] These patients are included in the fusion rate calculations but are otherwise considered as failures for clinical trial purposes.
[4] Patients due for follow up at that period who had secondary surgeries for reasons other than nonunions are considered failures for clinical trial purposes.
[5] Includes 3 patients who did not receive study treatments due to surgical events.

H. Poolability of Treatment Groups

All patients involved in the clinical trial of the INTER FIX™ Threaded Fusion Device, regardless of treatment group, were enrolled under the same inclusion/exclusion criteria. To substantiate the comparability of the randomized INTER FIX™ device patients and the nonrandomized INTER FIX™ device patients, the demographic characteristics, preoperative medical conditions, diagnostic imaging findings characteristic of degenerative disc disease, operative approach, and the location of the lumbar treated level were examined. Statistically significant differences ($p < 0.05$) were found in the following comparisons: operative approach, preoperative work status, and the preoperative diagnostic imaging findings of osteophyte formation of the vertebral endplates, scarring and/or thickening of the annulus fibrosis, ligamentum flavum, and/or facet joint capsule, and herniated nucleus pulposus.

Further statistical analyses showed that these variables were not associated with differences in the 12 month clinical outcomes of fusion, Oswestry Pain/Disability improvement, neurological status, or overall success, with the exception of herniated nucleus pulposus. For herniated nucleus pulposus, patients in the nonrandomized group had statistically significantly ($p < 0.05$) higher rates of overall success and 15 point Oswestry Pain/Disability improvement at 12 months.

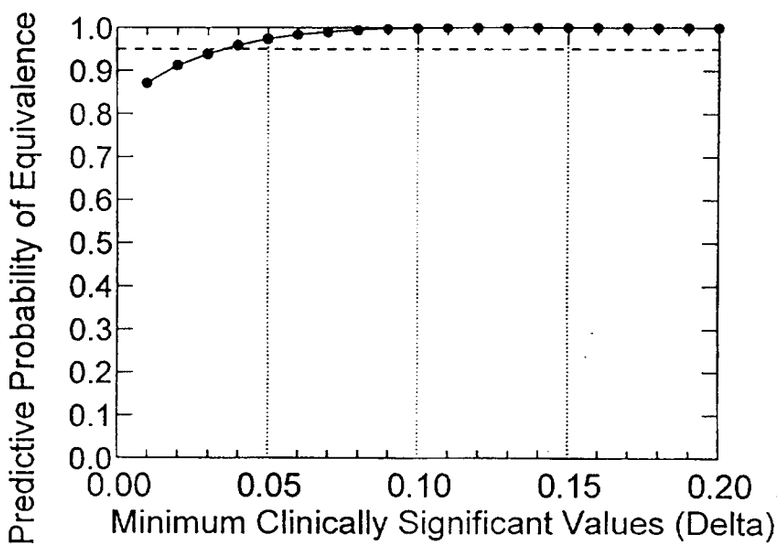
27

I. Bayesian Predictive Analysis

There were approximately 100 INTER FIX™ device patients who were not yet due for their 24 month postoperative evaluations at the time of the data analyses. A Bayesian statistical analysis was performed to determine the possible impact of these patients on the conclusions. Bayesian techniques can determine the probability that for the next 100 patients, a certain number will have a successful outcome on each clinical parameter. Since this trial was designed to show that the INTER FIX™ device is statistically no worse than the control, the Bayesian analysis provides the probability that equivalence would be shown when all the outstanding INTER FIX™ device results are obtained. Figure 1 presents the results of the Bayesian analysis.

Figure 1

Bayesian Predictive Probabilities of Equivalence*
For Overall Success - Includes Second Surgery Failures



*INTER FIX™ Device No Worse Than Control

Note: Overall success rates were based on patients with available data and did not include deaths, loss-to-follow-ups, or missing observations.

Predictive probabilities of equivalence were calculated for overall success rates for minimum clinically significant (delta) values ranging from 0.00 to 0.20. As shown in the figure above, the probability is greater than 0.95 (dashed line) that the INTER FIX™ Threaded Fusion Device results will still be statistically no worse than the

28

control results for overall success using a delta value of 0.04. Based on these results, it is very unlikely that the outstanding 24 month patients will significantly impact the existing results.

J. Safety Analysis

Safety analyses included all patients regardless of the completeness of their follow-up data or length of follow-up. Table I of this summary is a presentation of all adverse events which occurred in the randomized and nonrandomized INTER FIX™ device and control patients.

K. Clinical Trial Conclusions

The overall success for the INTER FIX™ device patients were statistically no worse than the control group patients at 24 months. The adverse effects and secondary surgical procedure rates were also comparable between the INTER FIX™ device patients and the control group patients.

XIV. CONCLUSIONS DRAWN FROM THE PREMARKET APPLICATION

The nonclinical (i.e., mechanical), preclinical (i.e., animal), and clinical data provide reasonable assurance of the safety and effectiveness of the INTER FIX™ Threaded Fusion Device for the treatment of patients with symptomatic degenerative disc disease (DDD).

XV. HISTORY OF PREMARKETING APPROVAL

The PMA application of the INTER FIX™ Threaded Fusion Device was first submitted on March 24, 1997 and filed by the FDA on May 2, 1997. A major amendment to the PMA in which the clinical results were updated was filed on October 14, 1997. The PMA was then presented to the Orthopedic and Rehabilitation Devices Advisory Panel on December 11, 1997. At that time, the Panel recommended, based on a 6-2 vote, that the application be found not approvable based on a desire for additional 24 month follow-up data.

Subsequently, FDA issued a PMA non-approvable letter on March 11, 1998 outlining several measures necessary to place the application in an approvable form. The most notable of these was the amassing of longer term follow-up data on patients, especially those in the randomized arm of the clinical trial. After an additional year of compiling follow-up data, another major amendment was filed on January 18, 1999. On May 14, 1999, FDA approved the PMA application for the INTER FIX™ Threaded Fusion Device and stipulated several post-approval conditions.

A. 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 INTER FIX™ Threaded Fusion Device.

The Panel discussed several issues which resulted in their recommendation against approval. These issues included the following:

1. The lack of data at the 24 month time point. This was the key issue for which the Panel recommended that the sponsor continue to follow the entire cohort until sufficient data was collect at the 24 month time point.

2. The study protocol proposed that success, when comparing the investigational and control devices, be based upon attaining equivalence. In the study, the equivalence was defined as the investigational device performing no more than 20% worse (delta = 0.2) than the control device at the 24 month timepoint. Sofamor Danek was asking that the panel consider the same definition of equivalence (based upon the same measurement tools) at 12 months, rather than 24 months. The Panel did not believe that it was appropriate to use the same delta of equivalence for different time points. In addition, the Panel did not believe that 12 month data was necessarily predictive of 24 month results.

3. Issues regarding appropriate success criteria for the Oswestry Disability Questionnaire. Specifically, the panel discussed an article by Beurskens, *et al.* in the journal Pain, which defined a clinically significant improvement as a decrease in an Oswestry score of 4-6 points (out of a possible 100). The Panel did not believe this was adequate clinically. As a result, a retrospective analysis was presented by the sponsor defining Oswestry success as a 15 point improvement in overall score.

Additionally, the panel also discussed issues dealing with the appropriate success criteria for the SF-36 and the validity of using CT scans for assessing fusion in the presence of morselized autograft.

B. CDRH Decision

CDRH agreed with the Panel's initial recommendations. On March 11, 1998, CDRH issued a not approvable letter for the INTER FIX™ Threaded Fusion Device. 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 subsequent meeting with FDA (December 22, 1997), the sponsor submitted a major amendment to the PMA (dated January 18, 1999). This amendment contained 24 month data on all the randomized patients as well as reanalyses and presentations of updated data.

C. Post Approval Study

As part of the conditions of approval, the sponsor agreed to the following:

1. Complete the follow-up requirements of the patients currently enrolled in the original clinical trial of the INTER FIX™ Threaded Fusion Device in accordance to the approved protocol.

2. In order to assess the long-term performance of the INTER FIX™ Threaded Fusion Device, please conduct a post-approval study to obtain a total of 6 years of postoperative data from a minimum of 100 patients.

3. Because of the unknown long-term device performance, particularly the resulting bony fusion characteristics, the post-approval study should also contain retrieval analyses of any INTER FIX™ Threaded Fusion Device that is implanted and subsequently removed.