Freedom® Lumbar Disc Wear Testing and Evaluation of Wear Debris in an Animal Model

CAUTION: Investigational device.
Limited by Federal law to investigational use.

Abstract

The Freedom Lumbar Disc (FLD) is a one-piece viscoelastic total disc replacement (TDR) intended to restore function to the spine in patients with degenerative disc disease (DDD). The materials used to manufacture the FLD are: titanium alloy, Ti-6Al-4V (ASTM F-136), commercially pure titanium (ASTM F67 Grade II), a urethane adhesive, and CarboSil™ TSPU, a silicone polycarbonate urethane polymer with silicone surface-modifying end groups.

Wear testing was conducted to characterize the wear that may be generated by the FLD in clinical use. A particulate study in rabbits was conducted to evaluate the local reaction and toxicity associated with FLD wear debris.

The Freedom Lumbar Disc generated wear within the wear rates of the competitive total artificial discs on the U.S. market. However, the size of FLD particulate was significantly larger and therefore less likely to induce a pro-inflammatory response than the particulate from competitive TDRs.

Particulate used for a rabbit study, which was worst case for particle size and represented doses of 98 and 980 years' worth of particulate debris, was found to be non-toxic. Additionally, particulate injected into the epidural space did not translocate to other locations or organs in the body.

Introduction

The Freedom Lumbar Disc (FLD) was designed to restore function to the spine in DDD patients in order to reduce or eliminate disabling pain, promote recovery and return to work when applicable, and potentially avoid degeneration of the adjacent lumbar segments.

The FLD is a one-piece viscoelastic total disc replacement (TDR) consisting of an elastomeric core bonded to titanium retaining plates. The FLD retaining plates and endcaps are manufactured from titanium alloy. End caps are locked into the retaining plates prior to implantation. The FLD core material is CarboSil™ TSPU, a silicone polycarbonate urethane thermoplastic elastomer.

In the assembled device, the retaining plates are mechanically and chemically adhered to the core with proprietary bonding techniques. This provides superior bond strength along the metal-to-core interface and low internal retained stresses within the core.

Wear testing of TDRs is conducted to characterize the amount and morphology of wear debris that may be generated *in vivo*. The ASTM method for wear testing, ASTM F 2423-05, "Standard Guide for Functional, Kinematic, and Wear Assessment of Total Disc Prostheses" is often used. This method combines a high lifting compressive load with the maximum ranges of motion in flexion, extension, lateral bending and rotation cited in the clinical literature. Studies have shown that the range of motion of the lumbar spine decreases with increasing compressive load (Janevic). As a result, the ASTM method places the device under range of motion and load combinations that intervertebral disc devices never experience *in vivo*.

The ASTM method specifies 10 million cycles in each of flexion/extension, lateral bending and rotation, with each conducted under an axial compressive load. Hedman's estimate of 125,000 significant bends per year for the average person is widely used to determine simulated life from wear testing. Flexion/extension, lateral bending and rotation are all considered to be significant bends. Thus, the tests specified in ASTM and ISO methods produce the equivalent of 240 years of significant bends.

Since there is always a concern that wear debris from implanted medical devices may cause adverse local or systemic reactions, a study was desired to evaluate the local reaction and toxicity of FLD particulate placed in direct contact with the spinal column. Since there was no formal regulatory guidance for this assay at the time it was conducted, the protocol was designed by NAMSA (Toledo, OH) to meet or exceed the guidelines provided in the "Draft FDA Guidance Document: Preclinical Testing Guidance Document for the Preparation of IDEs for Spinal Non-Fusion Systems". Fluoroscopically guided percutaneous injection was used to place either low or high dose FLD particulate samples or control samples in the epidural space of each rabbit. Animals were then monitored for either three or six months post-operatively, and pathological and histological analyses were conducted upon termination.

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Materials & Methods

Wear Testing

Wear testing was conducted at MarTest, Inc. (Cincinnati, OH), and followed ASTM F2423-05, "Standard Guide for Functional, Kinematic, and Wear Assessment of Total Disc Prostheses".

Three discs were tested in flexion/extension to 10 million cycles and then in coupled lateral bending and rotation to 10 million cycles, all at a testing frequency of 2 Hz. Another three discs were tested in reverse order. All testing included a constant axial compressive load of 1,200 N. Flexion/extension tests were conducted in load control to ±10 Nm, lateral bending was conducted in load control at ±12 Nm, and rotation was controlled to ±3°. Flexion/extension and lateral bending tests were conducted under load control because load control is more physiologic; the discs are loaded during daily activities and respond to those loads with motion. Rotation tests were conducted in displacement control because load control, as specified in the ASTM standard (± 10 Nm), resulted in excessive, non-physiologic (±15°) motion of the FLD. *In vivo*, rotation of the intervertebral discs is limited by the facets to approximately ± 3°; therefore, this was felt to be the more appropriate testing option.

All tests were conducted in enclosed 37°C phosphate buffered saline environments; therefore, no mixing of test environments between samples occurred.

Two FLD devices were tested as unloaded controls. A previous study of the FLD comparing loaded (1,200 N axial compression) vs. unloaded controls demonstrated no significant difference between device weights for loaded vs. unloaded controls.

Wear Analysis

Solution samples were collected by MarTest for each test device after each five million test machine cycles throughout testing and sent to BioEngineering Solutions Inc. (Oak Park, IL) for analysis. A total of 20 solution samples were analyzed, and all sample processing was conducted in a class II sterile environment. Each solution was filtered at 0.2 µ, centrifuged to collect the sediment (particles) for further analysis, and ultra-sonicated to de-flocculate particles.

Laser diffraction particle analysis (LALLS) was conducted for quantitative analysis of particle size. Scanning electron microscopy (SEM) with EDAX was conducted for qualitative analysis of particle shape. All particle sizes were given in equivalent spherical diameter (ECD) based on a volume analysis and a number analysis.

Particulate Study in Rabbits

FLD polymer cores were sent to the University of Florida Particle Engineering Research Center for cryogenic grinding into particulate samples. Biomechanical testing of the device did not generate enough particulate for use in a rabbit study. Therefore, the Preclinical Testing Guidance Document for the Preparation of IDEs for Spinal Non-Fusion Systems (Draft; 01/28/04) was used to determine the target particle size and doses for cryogenic grinding of particulate: The target particle size was 0.5 µm to 10 µm, with a median particle size of 5 µm; The target low and high doses were one and ten million particles, respectively. The samples generated had either 1.27 or 12.7 million particles in the size range of 1 to 15 µm, and 124 million or 1.24 billion particles in the size range of 0.1 to 15 µm. Additional particles outside of those size ranges were also present in the samples, providing a total of 308 million and 3.08 billion particles in the low and high dose samples, respectively. The particulate samples had a number average particle diameter of 0.1 µm and a volume average particle diameter of 11.1 µm.

The particle size data for particulate used in the rabbit study is summarized below:

Table 1: Particulate Study in Rabbits: Particle Number Summary

Number of Particles in the desired range of 1 – 15 µm	High dose: 12.7 million particles, 1 – 15 µm range Low dose: 1.27 million particles, 1 – 15 µm range
Number of Particles in the range of 0.1 – 15 µm	High dose: 124 million particles, 0.1 – 15 µm range Low dose: 1.24 million particles, 0.1 – 15 µm range
Number of Particles in the complete range of particle sizes generated	High dose: 3.08 billion particles, total range Low dose: 308 million particles, total range

FLD particulate samples consisted of particles suspended in 1,500 ppm Pluronic F-127/molecular grade water. The control article consisted of 1,500 ppm Pluronic F-127/molecular grade water. The low dose test articles were prepared by taking 1.0 ml aliquots from each of two sample vials and combining them. The combined low dose aliquots were mixed with 2.0 ml ISOVUE-M 300, giving a dose of 1.27 million particles (in the size range of 1 to 15 µm) when 200 µl was injected. High dose samples were prepared in the same manner, taking samples from high dose sample vials. Control doses were prepared by taking 1.0 ml aliquots from each of two sample vials of the control article and combining. The combined control dose aliquots were mixed with 2.0 ml ISOVUE-M 300.

The particulate study was conducted by NAMSA (Toledo, OH) in New Zealand White rabbits to evaluate the local reaction and/or toxicity associated with particulate debris generated from the polymer core of the FLD when placed directly within the epidural space via percutaneous injection. This study also examined the potential for translocation of wear debris and any associated reaction to the material. These effects were assessed by examination of clinical and neurological observations, hematological, histological, and gross pathologic methods.

A total of thirty-six animals were implanted for this study; three material groups at each of three and six month durations, with six rabbits per dose per duration per material group. The material groups were low dose, high dose and control. Each animal was injected with either the control solution mixed 1:1 with ISOVUE-M 300® radiopaque contrast solution, low dose test sample, or high dose test sample. Test sample particles were suspended in ISOVUE-M 300 to minimize coagulation of particulate so that the solutions could be injected into the rabbits.

For all groups, the suspensions were injected using fluoroscopic guidance into the epidural space of the spinal column at the lumbar region (L4-L6). A syringe was used to draw up the designated solution (low dose, high dose, or control). The suspension was vortexed immediately prior to aspiration. The dose volume was approximately 200 µl. Air bubbles were removed. The syringe was attached to the fluoroscopically placed needle quickly to minimize the time between aspiration and injection and injected into the epidural space. Approximately 100 µl of ISOVUE solution was then injected to rinse the test suspension from the needle lumen. Fluoroscopic images were saved to document the location of each injection.

Neurobehavioral observations were conducted at pretreatment, days 1 through 14 following surgery, and weekly thereafter. Specific findings related to attitude, posture, and locomotion were recorded. Animals were observed daily for general health, and special attention was made to note any evidence of neurological deficit or other neurological or musculo-skeletal abnormality. Body weights were recorded for each rabbit prior to the injection procedure, weekly for the first month, monthly thereafter, and at termination.

Upon termination, gross pathology, if any, was noted, and blood samples were taken. Local and distant tissues were harvested and analyzed histologically. Tissue samples included brain, heart, lungs, spleen, thymus, kidneys, adrenal glands, mesenteric, submandibular, and thoracic lymph nodes, gonads, the vertebral segments injected, along several vertebrae cranial and caudal to the site, the muscle tissue immediately adjacent to the injection site, and any tissues with visible gross lesions. Complete spinal segments, including all associated soft tissue, from T10 to S1 were dissected free and removed in toto. Multiple transverse sections of spinal segments from the injection site and caudal and cranial adjacent sections were histologically processed. Any abnormalities, such as blood clots, hemorrhage; fibrosis exceeding expected amounts, etc., were noted. Microscopically, the pathologist examined the processed sites for the presence of macrophages and multinucleated giant cells surrounding individual wear debris particles and any evidence of necrosis of tissues surrounding wear debris particles. The pathologist established inflammation scores and scores for the presence or absence of wear debris in organ sections. The propensity for the wear debris to migrate from the site was evaluated and compared to the responses in control animals. A semi-quantitative grading system was used during the histopathologic evaluation to assign a relative degree of severity to any observed changes.

Results

Wear Testing

Five test specimens reached 30 million device cycles (10M flexion/extension + 10M lateral bending + 10M rotation) with no functional failures. One specimen in the group tested first in lateral bending/rotation was lost during the first 10 million cycles due to part damage caused by a power outage. Per Hedman's estimate of 125,000 significant bends per year, 30 million device cycles corresponds to 240 years of simulated significant bends.

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The data shows that the devices lost an average of 0.07 g weight over 30 million device cycles of wear testing. Dimensionally, the parts lost an average of approximately a quarter of a millimeter in height over 30 million cycles, while the periphery dimension increased by approximately three quarters of a millimeter. These small dimensional changes demonstrate the good hysteresis (recovery) of the Freedom Lumbar Disc device.

Table 2: Summary of Device Changes During Wear Testing

Measurement	Mean Change for Test Group (n=5)	Mean Change for Controls (n=2)	Difference in Means
Weight	0.06 g loss	0.01 g gain	0.07 g
Posterior Height	0.26 mm loss	0.02 mm loss	0.24 mm
Anterior Height	0.28 mm loss	0.03 mm gain	0.31 mm
Lateral Length	0.84 mm gain	0.01 mm gain	0.83 mm
A/P Length	0.68 mm gain	0.04 mm gain	0.64 mm

The following plots show the data for each specimen and for each measurement (left) and mean data (right). Note that data points at 10.5 million cycles, which may appear to be spikes in the data, actually represent measurements taken after removal of devices after the first test at 10 million cycles, drying, and a repeat pre-conditioning step prior to initiation of the second set of 10 million cycles in the other test mode.

Figure 1: FLD Weight over 30 Million Device Cycles (20 Million Machine Cycles)

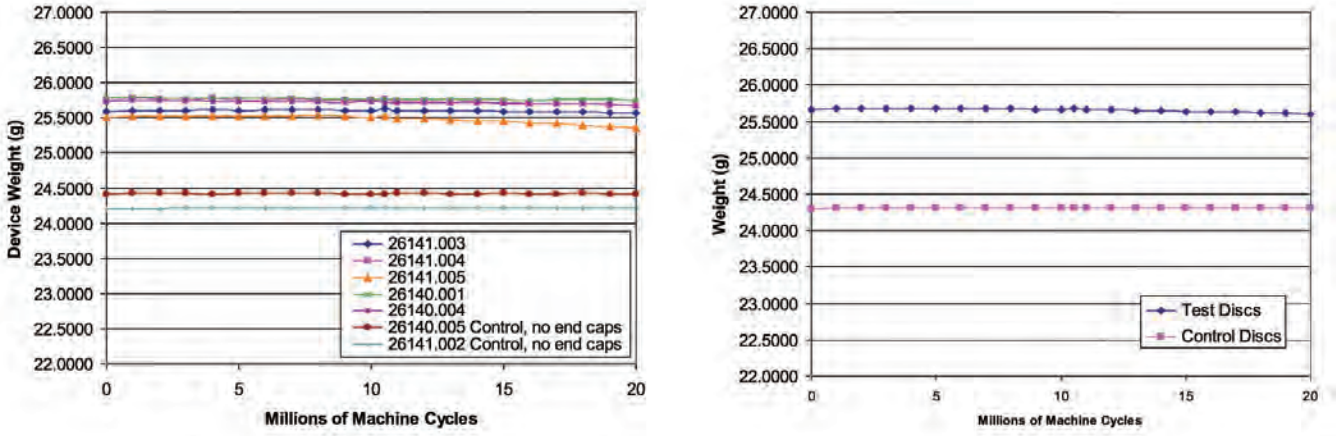


Figure 2: FLD Posterior Height over 30 Million Device Cycles (20 Million Machine Cycles)

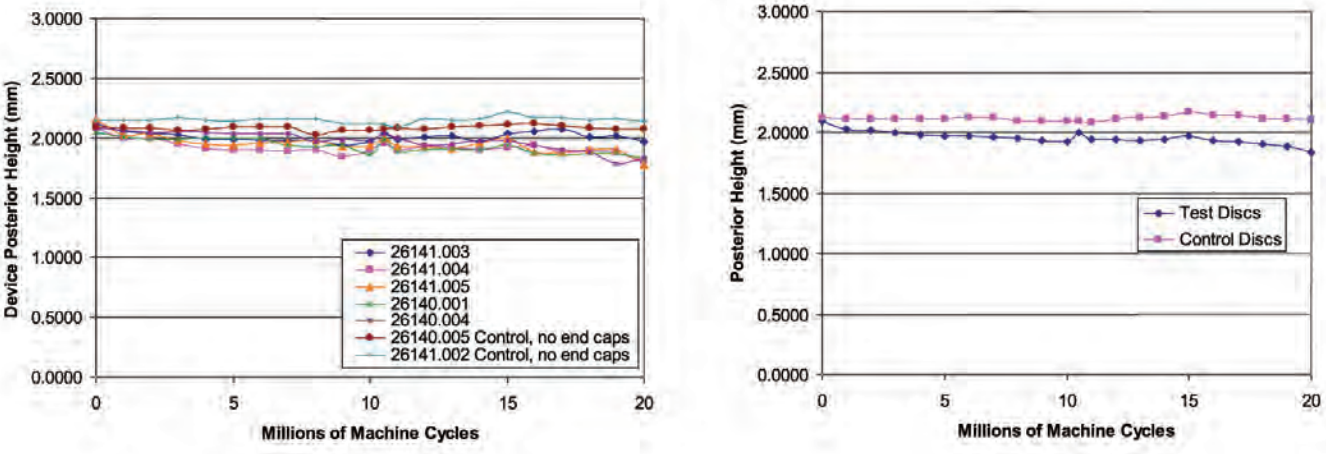


FIGURE 3: FLD ANTERIOR HEIGHT OVER 30 MILLION DEVICE CYCLES (20 MILLION MACHINE CYCLES)

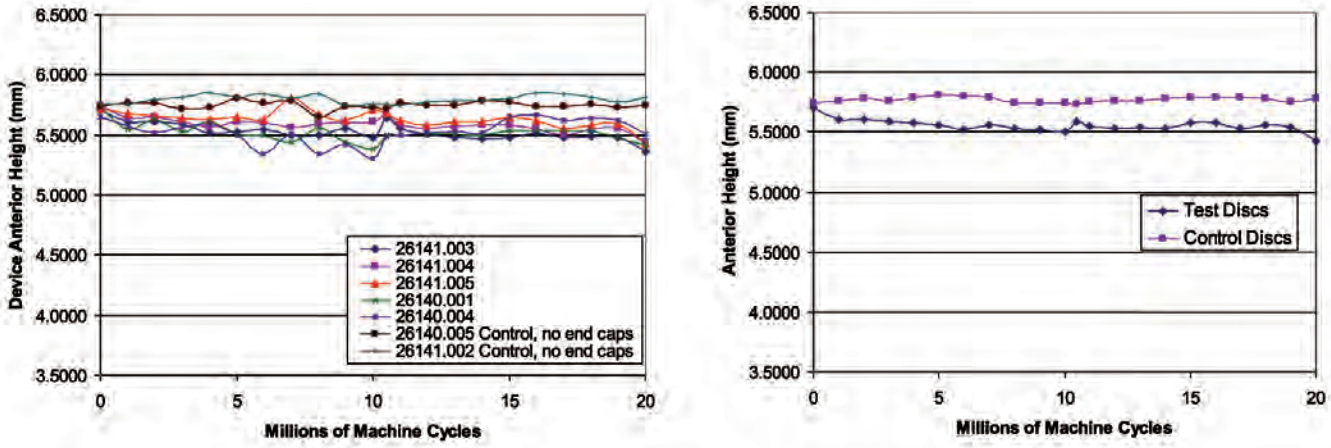


FIGURE 4: FLD LATERAL LENGTH OVER 30 MILLION DEVICE CYCLES (20 MILLION MACHINE CYCLES)

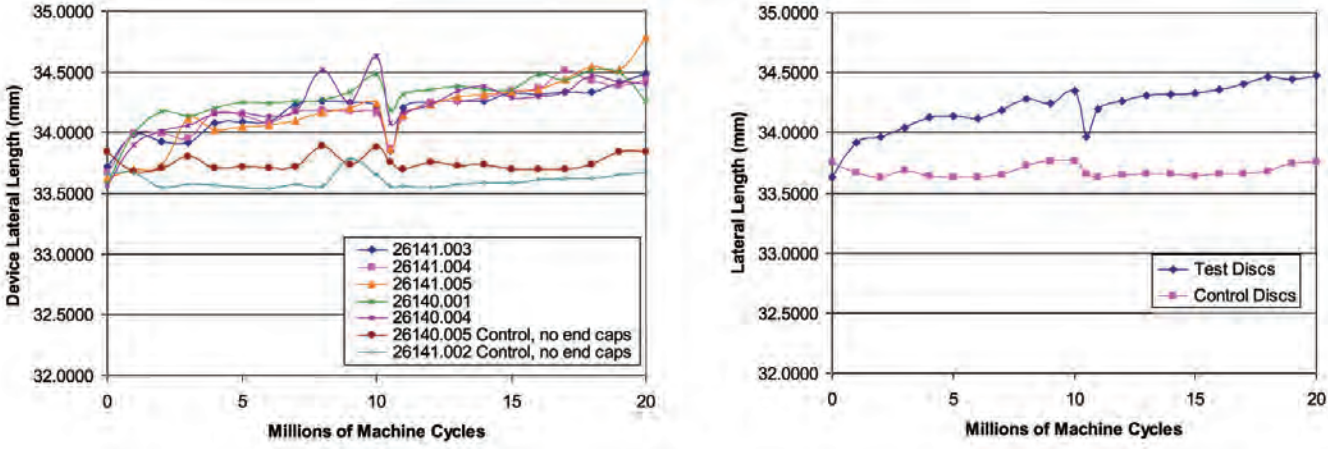
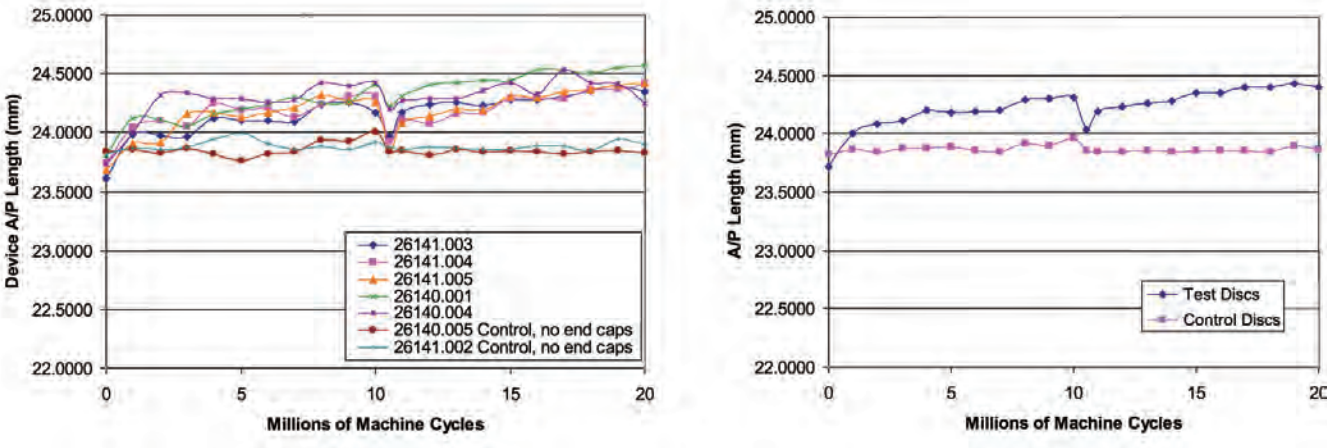


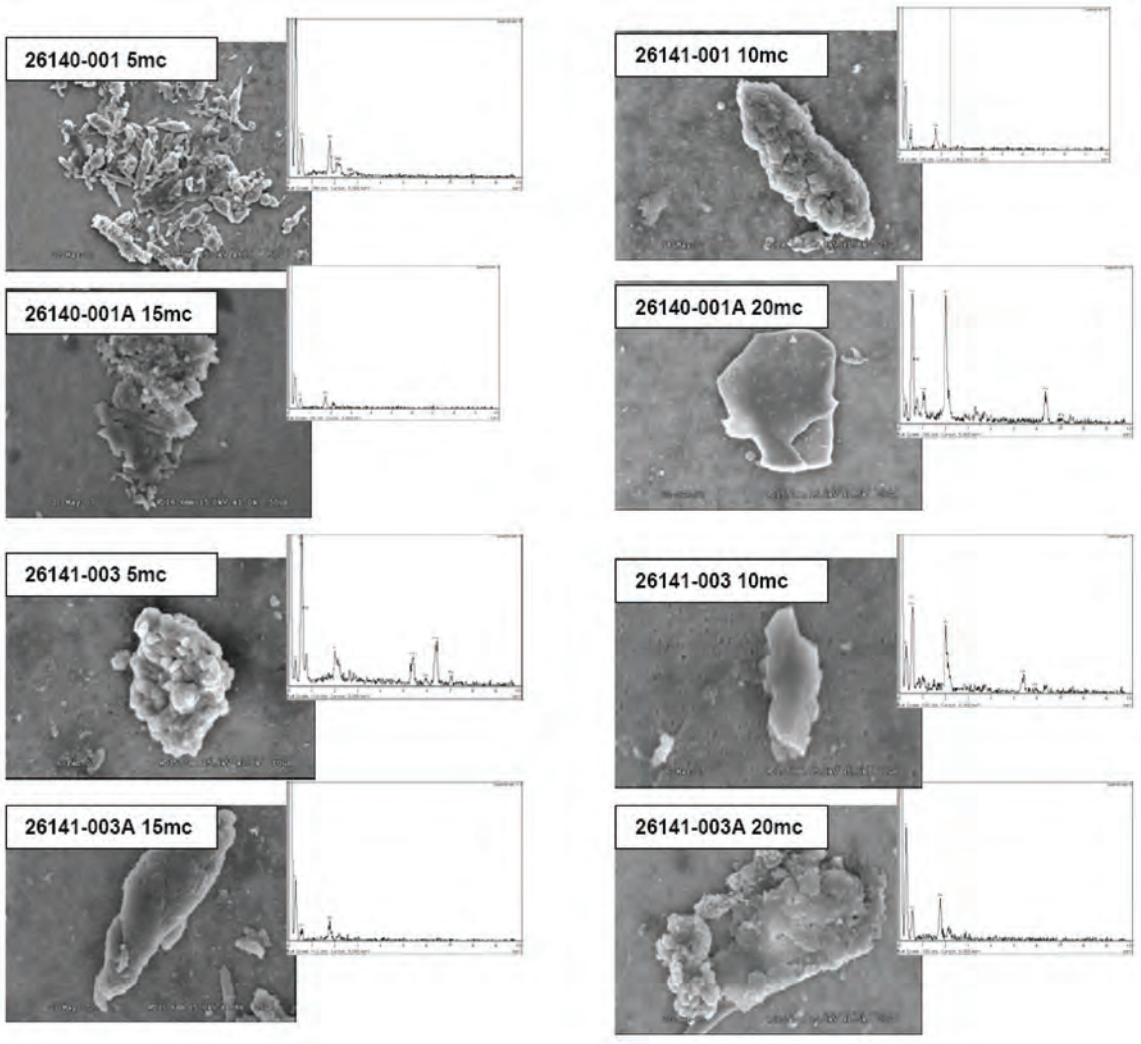
FIGURE 5: FLD A/P LENGTH OVER 30 MILLION DEVICE CYCLES (20 MILLION MACHINE CYCLES)



Wear Analysis

For the twenty solution samples tested, the number average particle diameter was 1.90 µm, with a range of 0.80 to 6.92 µm, and the weight average particle diameter was 48.66 µm, with a range of 23 to 76 µm. The average mass of particulate per million cycles of wear testing was 1.70 mg. Examples of particle shape are shown in figure 6.

Figure 6: Examples of Typical Particles from Wear Testing using SEM (Hallab 7/9/07)



Particulate Study in Rabbits

There were no significant complications during surgery. Clinical abnormalities noted during the study were mild and not directly attributable to any property of the test article. Body weight data was considered clinically acceptable following treatment. Macroscopic observations were incidental in nature and considered unrelated to treatment. There was no evidence of neurologic deficit or other neurologic or musculo-skeletal abnormalities following the surgical procedure. Organ weights and organ/body weight ratios were similar between and within test and control groups. There was no biologically or statistically significant differences in hematological parameters between any of the various test and control groups, and all mean values were within a normal expected range. There was no evidence of any inflammatory response, and all hematological parameter values were considered

equivalent between treatment groups and intervals. Microscopic evaluation of the injection sites revealed some wear debris from the injections, but no evidence of toxic or inflammatory responses to the test article. Based on the examined tissues, there was no evidence that the particulate migrated from the implant site. The tissues showed no evidence of a test article associated response.

In summary, there was no evidence of neurotoxicity, systemic toxicity, or local effects associated with treatment with the low or high doses of test material particulate. There was also no evidence of translocation of the wear debris.

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Discussion

In order to predict in vivo function and wear, a correlation of the number of wear testing cycles to the number of years in-vivo is desired. Hedman et.al., estimated that the average person experiences 125,000 significant bends in flexion/extension per year. It is assumed that a significant bend in flexion/extension is a full-range of motion bend. It is also assumed that a full-range of motion bend in rotation or lateral bending is a significant bend. As such, each cycle of any of flexion/extension, lateral bending and rotation is equal to one significant bend. Therefore, a test which includes 10 million cycles of each of flexion/extension, lateral bending and rotation produces 30 million total cycles. Per the estimate of 125,000 significant bends per year, each 5 million cycles is equivalent to 40 years of significant bends, ten million cycles is equivalent to 80 years of significant bends, etc., and 30 million cycles is equivalent to 240 years worth of significant bends.

Table 3 presents a comparison of the wear of FLD to that of Charité and ProDisc, as reported in their respective SS&Es (DePuy Spine and Synthes Spine).

Table 3: Summary of FLD Wear Rates vs. ProDisc-L vs. Charité

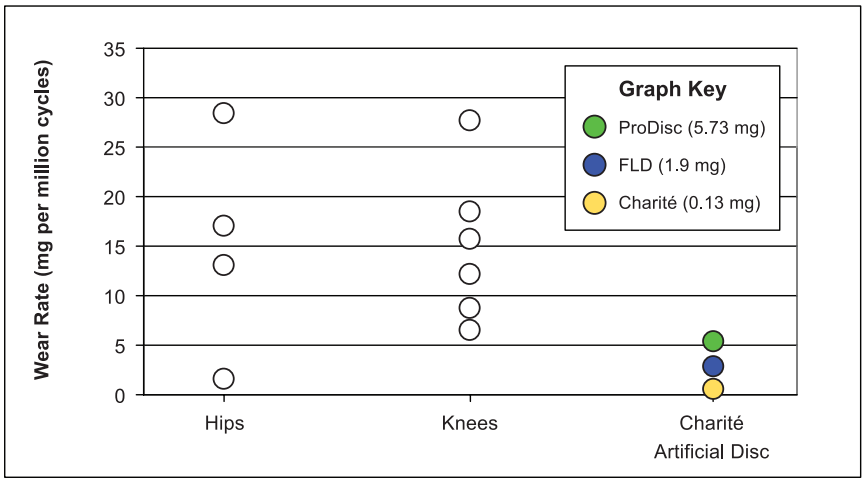
Device	Test Description	Total Number Of Device Cycles	Wear Rate (Mass Loss Per Million Cycles)	Number Average Particle Diameter
FLD	ASTM – 10M flex/ext + 10M lat bend/rotation	30 million	1.70 mg	1.90 µm
ProDisc-L	ISO – 10M flex/ext + lat bend + rotation	30 million	5.73 mg	0.44 µm
Charité	ASTM – 10M flex/ext + rotation, OR 10M lat bend + rotation	20 million	0.11 mg	0.2 µm

Even though the wear test methods were all somewhat different, the wear rate of the FLD was more than three times lower than that of the ProDisc-L. The FLD wear rate was higher than that of the Charité disc, possibly due to the fact that the FLD devices were tested to 30 million device cycles, while the Charité devices were tested to only 20 million device cycles.

The FLD wear testing generated a larger mean particle size (1.90 µm) than did Charité (0.2 µm) or ProDisc (0.44 µm) testing. As noted by Dr. Nadim Hallab of BioEngineering Solutions, a decrease in particle size has been found to result in an increase in bioreactivity (resultant biologic pro-inflammatory activity). Thus, the smaller particles from the ProDisc-L or Charité devices would be more likely to induce a pro-inflammatory response than the larger FLD particles.

In a 2006 article summarizing the wear assessment of the Charité Artificial Disc (Serhan), the wear rate of the Charité Disc was compared to the wear generated by hip and knee artificial joints. Figure 7 illustrates the comparison, with additional data added for ProDisc and FLD.

Figure 7: Comparison of Wear from FLD to Wear from Charité, ProDisc, Hip Implants and Knee Implants



The clinical evidence provided in the Charité and ProDisc clinical studies, as well as the clinical wear information for hip and knee implants, demonstrates that the benefits of joint replacements outweigh the residual risk of wear debris.

the high and low doses used in the FLD rabbit particulate study represent doses of approximately 98.4 and 984 years of wear debris, respectively.

Based on the particulate doses given to the rabbits, the number of particles generated per million cycles during the wear testing, and the human to rabbit weight ratio of 75 kg / 3.2 kg, the high and low doses used in the FLD rabbit particulate study represent doses of approximately 98.4 and 984 years of wear debris, respectively. Note that this is a conservative estimate, as the wear testing is considered to be an exaggeration of the true wear rate due to the non-physiologic loading specified.

The particulate generated during biomechanical testing had number and volume average particle diameters of 1.90 and 48.66 µm, respectively. A comparison of the biomechanical testing and rabbit study particulate samples was conducted by Dr. Hallab of BioEngineering Solutions. Dr. Hallab found that, based on prior research regarding particle size and bioreactivity, the manufactured particles used for the rabbit study would be more likely to induce a pro-inflammatory response than the particles generated during biomechanical testing. The cryogenically ground particles therefore provided a worst case scenario for the rabbit study. The particulate generated from the FLD during wear testing had a larger average particle diameter, and would therefore be less likely to induce a pro-inflammatory response than the cryogenically ground particulate used in the rabbit study.

Per Dr. Nadim Hallab:

> "The manufactured particles … (particles generated for rabbit study), with a particle size of 0.1um (mn), are well below that indicated by a similar analysis of simulator fluids… (particles generated during wear testing), at 1.9um, by approximately 10x. The differences in bioreactivity due to size differences at the submicron vs near micron diameters are incompletely understood. However there have been reports that suggest that a decrease in particle size results in an increase in bioreactivity (resultant biologic pro-inflammatory activity)…. Thus the manufactured particles would be more likely to induce a pro-inflammatory response than particles observed in simulator fluids. Thus testing the FLD particle represents a conservative approach to testing particles of FLD in a given animal model and can be viewed as a worst-case scenario of implant debris."

The number and weight average particle diameters of particulate from wear testing and particulate generated for the rabbit study are summarized in the following table:

Table 4: Particle Size Summary: Particles Generated for Rabbit Study vs. Particles Generated During Wear Testing

	Particles Generated for Particulate Study in Rabbits	Particles Generated During Wear Testing
Number Average Particle Diameter (μm)	0.1	1.90
Weight Average Particle Diameter (μm)	11.1	48.66

Conclusions

The Freedom Lumbar Disc generated wear within the wear rates of the competitive total artificial discs on the U.S. market. However, the size of FLD particulate was significantly larger and therefore less likely to induce a pro-inflammatory response than the particulate from competitive TDRs.

Particulate used for a rabbit study, which was worst case for particle size and represented doses of 98 and 980 years' worth of particulate debris, was found to be non-toxic. The study demonstrated no evidence of neurotoxicity, systemic toxicity or local effects. Additionally, particulate injected into the epidural space did not translocate to other locations or organs in the body.

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