# Biocompatibility of the Freedom® Lumbar Disc and Freedom® Cervical Disc

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

# Abstract

The Freedom® Lumbar Disc (FLD) and Freedom® Cervical Disc are one-piece viscoelastic total artificial disc implants for patients with degenerative disc disease (DDD).

The evaluation of the materials in the FLD and FCD included a full battery of tests specified in the International Organization for Standardization (ISO) 10993, Biological Evaluation of Medical Devices. This battery included many standard short term tests, as well as muscle implant studies, chronic and sub-chronic toxicity studies, and a full battery of material characterization (extraction) studies. Although the results of the genotoxicity studies demonstrated that the materials were nonmutagenic and not genotoxic, a carcinogenicity study in *ras*H2 transgenic mice was also conducted. Additional studies were conducted to evaluate the potential for lipid uptake or *in vivo* use to alter device properties and to evaluate the local reaction or toxicity of particulate debris generated from the polymer core of the FLD or FCD and the potential for translocation of wear debris.

The Freedom Discs are biocompatible.

The studies conducted demonstrate that the Freedom Discs are biocompatible. Results show no evidence of cell lysis, toxicity, delayed dermal contact sensitization, or systemic toxicity. Test devices were found to be non-pyrogenic, not genotoxic, and a non-irritant. The device materials were also found to be non-carcinogenic.

The materials tested… were found to be good candidates for biomedical applications and appropriate for their intended application.

Materials characterization, via exhaustive and exaggerated extractions of the FLD device and/or component materials of concern found no toxicological concerns for any leachate found at their respective levels. After toxicological assessment of each chemical substance using published toxicity data, as well as the possibility of interaction of more than one leachate, the evidence predicted material safety and device biocompatibility. The materials tested, including "worst-case" polymer/primer/polymer samples and FLDs, were found to be good candidates for biomedical applications and appropriate for their intended application.

Investigational Device Exemption (IDE) approved by FDA.

Additional studies determined that neither prolonged soaking in a lipid environment nor simulated *in vivo* use (via long term compression fatigue testing) cause changes in the properties of the FLD or FCD. Additionally, if particulate should be generated by the FLD or FCD *in vivo*, there would be no expected neurotoxicity, systemic toxicity, or local effects and no translocation of the wear debris. These studies were presented to the U.S. Food and Drug Administration (FDA) in support of an Investigational Device Exemption (IDE) submission, which was subsequently approved by FDA.

## Introduction

Symptomatic degenerative cervical and lumbar discs are frequently encountered diseases of the spine. For patients who cannot be treated successfully with conservative care, spinal arthrodesis or disc arthroplasty may be performed. While fusion is the conventional surgical treatment, it has limitations. Spinal fusion is a palliative rather than a curative procedure, and complications may arise, such as bone graft donor pain, prolonged recuperation, pseudoarthrosis, accelerated degeneration at adjacent levels, and instability. The published data indicate that only about 75% of fusion patients get any clinical benefit, and that only half will experience major or complete relief of pain or recovery of function. Anticipated re-operation rates within ten years are reported to be between 10% and 25%. The well-documented problems with fusion surgery have led surgeons and patients to seek different solutions.

The most promising alternative, particularly for patients in the later stages of the degenerative process, is total disc replacement. An ideal prosthetic disc will replicate the native function of the natural disc, including three dimensional motion, dynamic stiffness, load sharing capability, and proper maintenance of the lordotic curve. The elastomeric core material of the Freedom discs provides this critical combination of properties. The polymer core is comprised of a silicone polycarbonate-urethane; a viscoelastic material that has been optimized especially for use in the spine and in conjunction with the unique FLD and FCD designs. Its mechanical characteristics have been adjusted to replicate those of the natural disc so that the native function of the functional spinal unit (FSU) is re-established.

Although the biocompatibility of polycarbonate urethane and silicone have been demonstrated separately, and products incorporating them exist on the market, the biocompatibility of the copolymer had not previously been proven. The objective of this paper is to demonstrate the biocompatibility of the Freedom Lumbar Disc and Freedom Cervical Disc.

## Materials

Material specimens were manufactured for all short term biocompatibility testing to represent an exaggeration, or worst-case sample, of polymer and adhesive, with no titanium. The sample configuration was considered worst case due to the increased surface area of exposure of the polymer core. Test articles consisted of one-inch circular, 5 mm thick polymer/adhesive/polymer samples. For animal studies, test articles were designed and manufactured in dimensions appropriate for the model. For some tests, FLD finished devices were tested.


*Material specimens were manufactured for all short term biocompatibility testing, to represent an exaggeration, or worst-case sample of polymer and adhesive, with no titanium.*

## Methods

*International Organization for Standardization (ISO) 10993, Biological Evaluation of Medical Devices*

Biocompatibility studies were conducted according to the International Organization for Standardization (ISO) 10993, Biological Evaluation of Medical Devices, where applicable. All studies were conducted by NAMSA (Toledo, OH). The ISO 10993 biocompatibility test methods and samples are described in Table 1.

**TABLE 1: SUMMARY OF ISO 10993 BIOCOMPATIBILITY TEST METHODS**

| BIOLOGICAL EFFECT | TEST | TEST METHOD | TEST VEHICLE |
|---|---|---|---|
| Cytotoxicity | ISO elution method: *in vitro* mammalian cell culture test | ISO 10993, Part 5: Tests for Cytotoxicity: in vitro Methods guidelines | Test article extract |
| Sensitization | ISO maximization sensitization guinea pigs | ISO 10993, Part 10: Tests for Irritation and Sensitization | Test article extract |
| Irritation | ISO intracutaneous study in rabbits | ISO 10993, Part 10: Tests for Irritation and Sensitization | Test article extract |
| Acute Systemic Toxicity | USP and ISO systemic toxicity in mice | ISO 10993, Part 11: Tests for Systemic Toxicity | Test article extract |
| Pyrogen | USP pyrogen in rabbits | ISO 10993, Part 11: Tests for Systemic Toxicity | Test article extract |
| Genotoxicity | Bacterial reverse mutation | ISO 10993, Part 3: Tests for Genotoxicity, Carcinogenicity and Reproductive Toxicity | Test article extract |
| Genotoxicity | In vitro chromosomal aberration in mammalian cells | | |
| Genotoxicity | Mouse bone marrow micronucleus | | |
| Muscle Implantation | ISO Muscle implantation in rabbits – 2 weeks | ISO 10993, Part 6: Tests for Local Effects after Implantation | 10 mm diameter test article |
| Muscle Implantation | ISO muscle implantation in rabbits – 12 weeks | | |
| Sub-Chronic Toxicity | Rat sub-chronic toxicity study following subcutaneous implantation – 4 weeks | ISO 10993, Part 11: Tests for Systemic Toxicity | 15 mm dia. devices (98X exaggeration factor) |
| Chronic Toxicity | Rat chronic toxicity study following subcutaneous implantation – 26 weeks | ISO 10993, Part 11: Tests for Systemic Toxicity | 15 mm dia. devices (98X exaggeration factor) |
| Carcinogenicity | 26 Week carcinogenicity study in the transgenic ras H2 mouse model | ISO 10993, Part 11: Tests for Systemic Toxicity | 10 mm dia polymer -adhesive-titanium test articles |

Extraction studies were conducted to characterize the FLD/FCD materials according to ISO 10993. An extraction study was completed to characterize the worst-case sample configuration described above. Additional extraction studies were conducted for several reasons: to evaluate the effects of different extraction conditions, as requested by the U.S. Food and Drug Administration (FDA); to demonstrate that D3, D4 and D5, toxic leachables that can be derived from silicone, could not be found among the device's extractables, and; to confirm that no MDA could be extracted from the device.

The polymerization of the FLD/FCD polymer includes a specific step to ensure that no $D_3$, $D_4$ or $D_5$ siloxane cyclics are present in the polymer. The silicone used in the polymerization of the polymer is stripped with a wiped film evaporator prior to the synthesis to remove any tetramers, pentomers, etc. Thus, the evaluations of FLD/FCD test articles for $D_3$, $D_4$ and $D_5$ were conducted to confirm that these cyclic compounds are not present in and therefore cannot be extracted from the Freedom Discs.

The methods for processing and handling the polymer were developed and are controlled to eliminate the possibility of MDA being generated in the polymer. MDA can form if water is present when urethane groups dissociate and the water reacts with free diisocyanate or if the polymer is processed under a combination of high heat and moisture. The synthesis of the Freedom polymer was designed to minimize the chance of free isocyanate and prevent urethane dissociation. The manufacturing and sterilization of the FLD and FCD were specified to ensure that the polymer remains dry throughout processing. Thus, the evaluations of FLD test articles for MDA were conducted to confirm that it is not present in and therefore cannot be extracted from the Freedom Discs.

*The methods for processing and handling the polymer were developed and are controlled to eliminate the possibility of MDA being generated in the polymer.*

To estimate the release rate of leachables, an elution study was conducted. Groups of test articles were extracted at 37°C for each of 7, 14, 21 and 28 days in polar (PW) and non-polar (50:50 PW/ACN) fluid environments. Analytical tests were then performed to evaluate the presence and characteristics of any inorganic or organic compounds leached from the Freedom Discs.

Two risk assessments were conducted (NAMSA) to assess the health risk from potential chemicals leaching from the test articles. The risk assessment process consisted of: identifying critical health end points; determining the Tolerable Exposure (TE) of the patient to the leachable substance, and; determining feasibility and applying benefit when appropriate. If the feasibility evaluation determined that the TE was both technically and economically feasible, the TE became the allowable limit. If not, further modification of the TE based upon benefit evaluation was performed.

The materials characterization test methods and test vehicles are summarized in Table 2.

**TABLE 2: SUMMARY OF MATERIAL CHARACTERIZATION TEST METHODS**

| BIOLOGICAL EFFECT | TEST | TEST METHOD | TEST VEHICLE |
|---|---|---|---|
| Initial Evaluation of Extractables | Exhaustive extraction for aqueous NVR using the USP plastics ratio | ISO 10993, Part -17: Establishment of Allowable Limits for Leachable Substances and Part 18 (draft): Material Characterization Extractables/ Leachables | 25 mm diameter polymer/ adhesive/ polymer test article |
| | Exhaustive extraction for non-aqueous NVR using the USP plastics ratio | | |
| | Determination of extractable semi-volatile organic compounds by GC/MS | | Test article extract |
| | Chemical analysis of test article extract for trace elements by ICP spectroscopy | | |
| Additional Evaluation of Extractables | USP Physicochemical test, aqueous extraction for NVR, ROI, heavy metals and buffering capacity using purified water | ISO 10993, Part -17: Establishment of Allowable Limits for Leachable Substances and Part 18 (draft): Material Characterization Extractables/Leachables | L-281612 FLD (composite device) |
| | Physicochemical test, non-aqueous extraction for NVR, ROI, turbidity and UV absorbance using 50/50 purified water/acetonitrile | | And |
| | GC/MS for the detection and quantitation of semi-volatile organic compounds | | 25 mm diameter polymer/ adhesive/ polymer test article For each test |
| | HPLC to evaluate the presence of 4,4'-methylene dianiline (MDA) | | |
| | IR scan of NVR | | |
| | GC/MS for volatile headspace analysis | | |
| | ICP spectroscopy scan of purified water extract for evaluation of trace elements/metals | | |
| Evaluation of Extractables Elution Profile | USP Physicochemical test, aqueous extraction for NVR, ROI, heavy metals and buffering capacity using purified water | ISO 10993, Part 18 – "Chemical Characterization of Materials" | 25 mm diameter polymer/ adhesive/ polymer test article |
| | Physicochemical test, non-aqueous extraction for NVR, ROI, turbidity and UV absorbance using 50/50 purified water/acetonitrile | | |
| | IR scan of NVR for identification, PW and PW/ACN extracts | | 7 and 28 Day extracts from test article |
| | HPLC of extracts for evaluation of MDA | | |
| | GC/MS of extracts to evaluate presence of semi-volatile organics | | |
| | Volatile headspace analysis of extracts by GC/MS for volatile organics (residual solvents and cyclic siloxanes) | | |
| | ICP scan of purified water extracts for trace elements/metals | | |
| Risk Assessments | Assessment of health risk from potential chemicals leaching from the test articles; assessed results from initial material characterization studies, additional extraction studies and elution study. | ISO 10993, Part 17: "Method for the Establishment of Allowable Limits for Leachable Substances", ISO 14971:2000(E): "Medical Devices – Application of Risk Management to Medical Devices", and Annex C: "Guidance on Risk Analysis Procedure for Toxicological Hazards" | |

A study of the lipid uptake of the Freedom polymer was desired to determine the effects lipid absorption would have on the polymer used for the core of the Freedom discs. Lipid absorption has been known to cause degradation, such as embrittlement, and diminish the mechanical properties of some polymers.

To determine if the Freedom polymer undergoes environmental stress cracking, crazing, or chain rupture due to hydrolytic degradation mechanisms during simulated *in vivo* use, several analyses were conducted on untested Freedom discs and Freedom discs that had been compression fatigue tested to ten or fifty million cycles. Another study objective was to evaluate the effect of simulated *in vivo* loading on potential leachate release. Analyses were conducted on discs and extracts to evaluate extractables and physical and mechanical properties. Since compression is the loading mode experienced most by intervertebral discs, devices which completed run-out compression fatigue testing were chosen for analysis as the closest *in vivo* simulation. Although some devices completed testing at loads higher than those seen *in vivo*, they were still used for these analyses.

A particulate study in New Zealand White rabbits was conducted to evaluate the local reaction and/or toxicity associated with particulate debris generated from the polymer core of the FLD or FCD when placed in direct contact with the spinal column via the percutaneous injection method. 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.

FLD polymer cores were cryogenically ground at the University of Florida Particle Engineering Research Center (Gainesville, FL) into particulate samples. 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.

Based on the particulate doses given to the rabbits, the number of particles generated per million cycles during the FLD wear testing, and the human to rabbit weight ratio of 75 kg / 3.2 kg, the high and low doses in the rabbit particulate study represent doses of approximately 98.4 and 984 years of FLD 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. Since the FCD wear rate was found to be lower than that of the FLD, the doses used in the rabbit study are exaggerated even more for the FCD.

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

The particulate later generated during FLD biomechanical testing had number and volume average particle diameters of 1.90 and 48.66 µm, respectively. A comparison of the two particulate samples was conducted by Dr. Nadim Hallab of BioEngineering Solutions (Oak Park, IL). 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 additional test methods and test specimens are described in Table 3.

**Table 3: Summary of Additional Test Methods**

| Test | Test Methods | Test Vehicle |
|---|---|---|
| Lipid Uptake | Determination of weight and dimensional changes of the test articles, determination of lipid content and free fatty acid after incubation (via Soxhlet extraction and titration), SEM analysis of the test articles to evaluate surface damage and tensile testing | Tensile specimens |
| Material Changes after Fatigue Testing | Physicochemical test, non-aqueous extraction for NVR, 50/50 PW/ACN, HPLC to determine molecular weight using GPC, IR of test article polymer and of extract residue for identification, thermal analysis using DSC, durometer hardness of the material, and SEM microanalysis of the polymer surfaces. | FLD and FCD untested and tested in compression fatigue to 10 or 50 million cycles |
| Particulate Study | Evaluation of wear debris in the rabbit spine, percutaneous injection method, 3 and 6 month intervals, utilizing NAMSA methods, with Preclinical Testing Guidance Document for the Preparation of IDEs for Spinal Non-Fusion Systems (Draft; 01/28/04) as a guide. | Cryogenically ground FLD polymer particulate |

## Results

### ISO 10993 BIOCOMPATIBILITY TESTING

The results of short term biocompatibility testing are summarized in Table 4.

**TABLE 4: SUMMARY OF ISO 10993 BIOCOMPATIBILITY TEST RESULTS**

| | |
|---|---|
| Cytotoxicity | Test extract: USP grade = 0 (no reactivity and no lysis).<br>Test extract showed no evidence of causing cell lysis or toxicity. |
| Sensitization | All animals appeared clinically normal throughout the study.<br>All dermal reaction scores were 0 (no erythema and no edema).<br>No evidence of sensitization.<br>No evidence of delayed dermal contact sensitization in the guinea pig. |
| Irritation | All rabbits appeared clinically normal throughout the study.<br>All injection sites appeared normal immediately following injection. Primary Irritation Score totals for each extract group were zero.<br>Primary Irritation Index Characterization for extracts was negligible.<br>No evidence of significant irritation. |
| Acute Systemic Toxicity | All body weight data were acceptable.<br>No mortality during the study.<br>All animals appeared clinically normal throughout the study.<br>No mortality or evidence of systemic toxicity from the test extracts. |
| Pyrogen | Total rise of rabbit temperatures during 3 hour observation period within acceptable USP limits.<br>No rabbit showed a temperature increase > 0.4°C above its baseline temperature.<br>The extract was nonpyrogenic. |
| Genotoxicity via Bacterial Reverse Mutation | Test article extract was nonmutagenic to *Salmonella typhimurium* tester strains TA98, TA100, TA1535 and TA 1537, and to *Escherichia coli* strain *WP2uvrA*. |
| Genotoxicity via In Vitro Chromosomal Aberration in Mammalian Cells | Toxicity was not observed for the test group.<br>Test article extract was not genotoxic to Chinese Hamster Ovary cells in the presence or absence of S9 metabolic activation. |
| Genotoxicity via Mouse Bone Marrow Micronucleus | All mice appeared clinically normal throughout the study.<br>Weight changes over the course of the study were normal.<br>Test article was not genotoxic to the mouse.<br>No evidence of cellular toxicity. |
| Muscle Implantation: 2 and 12 Weeks | All animals appeared clinically normal throughout the study.<br>Body weight data were acceptable.<br>No visible reaction at any test site.<br>Test article was classified as a nonirritant. |
| Sub-Chronic and Chronic Toxicity | No evidence of systemic toxicity following subcutaneous implantation in the rat.<br>Daily clinical observations, body weights, necropsy findings, organ weights and organ/body weight ratios within acceptable limits.<br>No changes in histopathology, hematology values or clinical chemistry values that were considered to be biologically significant or related to treatment with the Freedom test article.<br>No evidence of a treatment related response seen in microscopic evaluations of the selected tissues.<br>No significant difference in the cellular reaction between the control and test articles. |
| Carcino-genicity | No statistically significant differences in organ to body weight ratios between any of the treatment groups.<br>Incidence rate of tumors in the test group within the expected incidence rate.<br>No treatment-effects or gender-based treatment-effects found in the test group.<br>No tumors were found at the implantation sites in the test group.<br>No statistically significant difference in tumor incidence rates between the test and negative control groups.<br>Freedom test article did not demonstrate an increased incidence of tumor formation (tumorogenicity) compared to the negative control following subcutaneous implantation in a transgenic mouse model. |

### Material Characterization

The results of extraction and elution studies are summarized in Table 5.

**Table 5: Summary of ISO 10993 Material Characterization Results**

| | |
|---|---|
| Initial Material Characterization: Exhaustive Extractions | • Amount of extractable or released chemicals from the FLD found to be very low for both purified water and acetonitrile/PW 50:50 extracts.<br>• No significant amounts of extracted substances from the FLD or worst case polymer/primer/polymer samples.<br>• All of the amounts were significantly lower than the USP limit of ≤15 mg. |
| Additional Extraction Studies: Exaggerated Extractions | • No significant amounts of extracted substances from the FLD or worst case polymer/primer/polymer samples.<br>• Amounts of extracted substances from the FLD were consistently lower than those from the worst case samples.<br>• All of the amounts were significantly lower than the USP limit of ≤15 mg.<br>• Thus, the potential risk for patient exposure to extractables or leachables is very low.<br>• No MDA, $D_3$, $D_4$ or $D_5$ were found in any extract at any time point. |
| Elution Study | • NVR does not significantly increase between 7 and 28 days.<br>• The total amount of extracted substances reached its maximum at 7 days incubation in either the polar or non-polar extract. This finding demonstrates polymer stability: If the test articles had been prone to hydrolytic degradation, a steady and progressive increase in NVR would have been observed. |

### Risk Assessments

Polyurethane medical devices, which have been implanted in humans for over 25 years, have never been linked to cancer in humans. Additionally, the biological safety of the Freedom polymer and similar polyurethane polymers has been demonstrated in numerous studies in the literature. The Freedom polymer meets the requirements for long term implant device application and is safe for the intended application in the FLD and FCD.

There were no toxicological concerns for any leachate found at their respective levels. After toxicological assessment of each chemical substance using published toxicity data, as well as the possibility of interaction of more than one leachate, the evidence predicted material safety and device biocompatibility. The materials tested, including "worst-case" polymer/primer/polymer samples and FLDs, were found to be good candidates for biomedical applications and appropriate for their intended application.

*Polyurethane medical devices, which have been implanted in humans for over 25 years, have never been linked to cancer in humans.*

*The Freedom polymer meets the requirements for long term implant device application and is safe for the intended application in the FLD and FCD.*

## Additional Studies

### Lipid Uptake Study

There was no lipid uptake in the Freedom polymer after 20 or 100-day incubations in calf serum solution. There was also no difference in mechanical properties between Freedom polymer specimens incubated in calf serum vs. saline.

*…no lipid uptake in the Freedom polymer.*

### Material Changes after Simulated Use

Both mechanically tested and untested Freedom devices had the same level of extractants (NVR), suggesting that no detectable degradation, such as polymer scission, occurred during testing. The GPC results (molecular weight) indicated that the extracted chemicals were the same size and the dispersities (molecular weight distribution) were comparable between groups, demonstrating that mechanical testing did not result in any detectable degradation of the polymer or any change in leachates with loading. GPC results for the polymer samples indicated that biomechanical testing did not result in any significant shifts in molecular weight or distribution of molecular weights, giving predictive evidence of no detectable degradation.

Infrared scans showed that peak heights and band intensities were uniform and consistent for both samples, suggesting no degradation. The shore A hardness of polymer in the tested FLD was slightly higher than that of the untested FLD. It is theorized that the loss of approximately 0.2 mm during compressive fatigue testing to ten or fifty million cycles results in the slight increase in hardness at the surface of the polymer core. SEM analysis found no notable differences between tested and untested samples; no crazing and no tearing. Thermal analysis showed that there were no significant differences in thermal transitions, indicating no changes in the polymer due to fatigue testing.

*no evidence of degradation, polymer changes, or changes in leachates from÷ 10 to 50 years (simulated) in vivo use.*

Overall, there was no evidence of degradation, polymer changes, or changes in leachates from compressive fatigue testing of the FLD or FCD at physiologic and higher loads to ten and fifty million cycles, which simulates 10 to 50 years *in vivo* use.

### Particulate Study in Rabbits

Body weight data was clinically acceptable following 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 were 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 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. There was no evidence that the particulate migrated from the implant site, and the tissues showed no evidence of a test article associated response.

*no evidence of neurotoxicity, systemic toxicity, or local effects÷ no evidence of translocation of the wear debris.*

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, and there was no evidence of translocation of the wear debris.

# Conclusions

Through an extensive battery of testing, the Freedom Lumbar and Cervical Discs have been shown to be biocompatible and non-carcinogenic. Potential leachables from the devices are low and have been found to present no toxicological concern. The devices are not susceptible to lipid uptake. If particulate is generated, it is biocompatible and does not cause an inflammatory response. Long term simulated *in vivo* use does not change the material properties of the device.