

# Points to Consider in the Preparation of IDEs for Total Artificial Discs

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## Introduction

Orthopaedic spinal devices can be separated into two main types: fusion devices and non-fusion devices. Fusion devices consist of interbody fusion cages, vertebral body replacements, pedicle screw systems, and any other device that is intended to promote fusion of spinal elements to treat disorders of the human spine. Non-fusion devices are intended to stabilize the spine by providing limited motion, but without fusing the spine.

As the technology of spinal implants moves forward, the development of safe and effective devices that allow and preserve spinal segmental motion have moved to the forefront of Orthopaedic science. Based on the surge of scientific interest in the preservation of motion in the spine, particularly in the development of artificial disc technologies, this document strives to provide “points to consider” for developing appropriate pre-clinical and clinical trials to assure the safety of patients and the effectiveness of devices to relieve symptoms of spinal etiology and improve quality of life.

The purpose of this document is to provide “points to consider” to industry sponsors and FDA staff about important preclinical and clinical information, which should be presented in an Investigational Device Exemption (IDE) application for total intervertebral disc replacement systems (i.e., total artificial discs). FDA is issuing this document to help ensure consistency and understanding between FDA and sponsors when developing IDE submissions for total artificial discs. We hope this document will conserve FDA and industry resources and facilitate timely review.

This “points to consider” document is applicable only to total artificial discs. This document is **not** applicable to other types of spinal systems that are designed to allow some degree of motion in the spine, such as spinal stabilization systems using pedicle screws or other flexible implants *without* fusion, disc nucleus replacements, partial intervertebral disc replacements, any spinal joint replacements (e.g., facet joint replacement), any other joint motion sparing or replacing implants, and combination products that may include biologic or pharmaceutical materials. Because of the complexity of these devices and design-specific issues, sponsors are encouraged to submit pre-IDE submissions to ORDB to facilitate discussion regarding the important preclinical and clinical information required for an IDE application. Please contact the ORDB Branch Chief or contact Michael Courtney at (301) 594-2036 or via email at [michael.courtney@fda.hhs.gov](mailto:michael.courtney@fda.hhs.gov) for additional information regarding the pre-IDE submission process.

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This document does not pertain to class II or class III spinal implant devices requiring an IDE or clinical data which are intended for intervertebral body fusion systems, which may include cages, vertebral body replacement devices, or spinal vertebral body augmentation devices for vertebroplasty. Recommendations for the preclinical testing required for the preparation of IDE submissions for other spinal systems are provided in the “Guidance Document for the Preparation of IDEs for Spinal Systems” (<http://www.fda.gov/cdrh/ode/guidance/87.html>) and “Clinical Trial Considerations: Vertebral Augmentation Devices to Treat Spinal Insufficiency Fractures” (<http://www.fda.gov/cdrh/ode/guidance/1543.html>).

In this document, a spinal “system” is defined here as the complete implant configuration. A “component” is a single element in a system. “Construct” references are typically made when discussing testing. For the purposes of this “points to consider” document, “system” and “device” are used interchangeably.

This document does not establish legally enforceable responsibilities. Instead, this document describes our current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* means that something is suggested or recommended, but not required.

## **A. DEVICE DESCRIPTION**

In accordance with 812.25, adequate device description information should be submitted. Specifically, the following information, at minimum, should be provided for total artificial discs:

- a table that includes each component name and corresponding part number
- a complete written description of the individual components and how any components interconnect
- complete mechanical drawings with all dimensions and tolerances of each individual component and, if applicable, of the total system
- supporting magnified sketches or photographs of the total artificial disc attached to a spinal model
- a description of the material(s) and any voluntary material standard(s) to which the material(s) conform. Depending on the material, biocompatibility issues may need to be addressed. Biocompatibility information should be included in the Report of Prior Investigations section of the IDE
- a description of anticipated changes to the system
- a list of all instruments unique to the implantation of the subject system, the material and voluntary material standard to which they conform, and supporting magnified sketches or photographs of them

## **B. REPORT OF PRIOR INVESTIGATIONS**

Please refer to the Report of Prior Investigations section of the “Guidance Document for the Preparation of IDEs for Spinal Systems” (<http://www.fda.gov/cdrh/ode/87.html>) for full details.

A statement as to whether all nonclinical tests comply with the GLP regulations (21 CFR 58) should be provided. Otherwise, a rationale for noncompliance with GLP regulations should be provided.

### **1. CLINICAL DATA**

Please refer to Item 1. of the Report of Prior Investigations section of the “Guidance Document for the Preparation of IDEs for Spinal Systems” (<http://www.fda.gov/cdrh/ode/87.html>) for full details.

A description of how the prior investigations have influenced subsequent changes in device design, patient selection and/or surgical technique and instrumentation should be included within clinical data reports, where applicable.

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Please also refer to the “Clinical Data Presentations for Orthopedic Device Applications” (<http://www.fda.gov/cdrh/ode/guidance/1542.html>) for detailed descriptions of and sample tables for the items requested in this section.

## **2. ANIMAL DATA**

In many cases, clinical data are not available for the device or any of its components. Therefore, animal data may be needed to establish the relative safety of the subject system. Reasons for animal studies include but are not limited to: proof of concept; evaluation of different design concepts, surgical instrumentation and/or technique; identifying failure mechanisms; functional studies (such as maintenance of motion and/or disc height without fusion or subsidence); addressing biologic response to particle and substrate materials; dosing studies; biocompatibility; and toxicity.

Complete reports of any animal studies conducted on the subject system or components of it, whether adverse or supportive, that are relevant to the evaluation of the safety or effectiveness of the subject system should be included. The animal report should specify the purpose of the study and provide supporting pathological, histological, and radiological evaluations. These reports should include an executive summary of the evaluation by a certified pathologist. If testing was not done on the final, sterilized version of the device proposed in the IDE, the report should describe the differences between the version of the system used in the animal studies and that proposed in the IDE. A discussion with justification of why the results and testing should be considered meaningful should also be provided.

We recommend that the following information be included as part of a complete report of any animal testing:

- identification of the animal model and a rationale for the choice of animal model (e.g., relevance to human anatomy or disease)
- identification of the device components or particles used in the study and a rationale for why these were selected
- the evaluation timepoints of the study and a rationale for choosing these timepoints
- the number of animals evaluated at each timepoint and rationale for the number of animals chosen
- identification of the test control
- the results, and
- a discussion of the results in terms of the expected *in vivo* and clinical behavior of the device

Although animal studies may be necessary to address specific questions prior to human use, we recognize that choosing and validating an animal model is difficult because there is no perfect model. Many animal studies have involved sheep, goats, primates, dogs, or kangaroos. In choosing an animal model for evaluating the device, you should consider the anatomy and

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physiology, biomechanics, expected *in vivo* loads, etc. as compared to the human situation. Each animal model should be carefully considered based on the purpose of the study.

### ***Functional Animal Study***

For functional animal testing, we recommend that you perform all testing on sterilized components of the final device design. We also suggest that you use a control for your functional animal testing so that a frame of reference can be established for the performance of your device/materials.

The functional animal model should reflect the intended use of the device. This should be taken into consideration when developing your test model and determining the levels of implantation in the animals.

### ***Particulate Animal Study***

If the wear particulates of a material have not been comprehensively evaluated in the spine or at the indicated spinal level, then a study using a small animal model (e.g., rabbit) may be necessary. The objective of this study is to evaluate the local and systemic responses (e.g., biocompatibility, neurologic response, tissue response, and toxicity) to the particulate debris.

The wear particles used in the study should represent the size, shape, amount, and chemical composition of those expected from *in vivo* use (i.e., representative of particulates generated from bench-top testing). Regardless of the amount of debris generated from bench-top testing, at least one group of animals should receive a sufficient dose so that particles can be located during histologic analysis. If wear particles cannot be identified and located, it may not be possible to draw conclusions about either particle transport or the local tissue reaction to particles from your device. Based on literature and previous testing, we recommend a minimum of 10 million particles for this high-dose group, but a higher number may be necessary depending on particle size and composition. The histology results should account for the injected wear debris. For instance, if the particulates are implanted into the lumbar spine, then we expect that these particulates should be observed at the injection site and/or in other parts of the body.

Physical and neurological observations should be taken throughout the study. Animals should be sacrificed at 3 and 6 month timepoints, though longer timepoints might be needed depending on the material/device. A minimum of three (3) samples should be harvested from three (3) different areas of each organ/tissue evaluated for the minimum of the following areas: spinal region, paraspinal region, dura, and local lymph nodes. Depending on the materials and the level the implant is indicated, it may be necessary to evaluate additional tissue/organs such as spleen, kidneys, heart, liver, lung, and pancreas. An unbiased or independent toxicologist should harvest all samples and analyze the pathological slides generated from the samples.

References to animal studies in the literature may be appropriate for evaluating the biological response to wear particulate. However, a rationale should be included to explain how the particulate in the referenced animal studies are representative of those expected from *in vivo* use of your device (i.e., representative of particulates generated from bench-top testing).

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### ***Cytokine Analysis***

It may be appropriate to assess the potential for osteolysis by evaluating the cytokine response to wear debris. This testing could be accomplished through evaluation of the cytokine response during either a small animal particle implantation study or a functional animal study using, for example, the methods described by Cunningham et al<sup>1</sup>.

### **3. MECHANICAL DATA**

All total artificial discs require some mechanical testing or an acceptable rationale addressing why testing is not necessary in order to establish the relative safety of the subject system. The specific requirements for mechanical testing are influenced by the design, material, method of attachment to the spine, and patient indication.

Complete reports of any mechanical testing conducted on the subject system or its components, whether adverse or supportive, that are relevant to the evaluation of the safety or effectiveness of the subject system should be included. A comprehensive summary of all mechanical testing should be included in addition to complete reports of each test. The following elements, at minimum, should be included as part of each test report:

- identification of the components that comprised the constructs or subconstructs tested
- identification of any test standard(s) to which the testing conforms, including identification and justification of all deviations from the test standard
- the testing set-up
- the testing procedures
- rationale that testing involved a worst case design, material, and if necessary, manufacturing-related processing
- rationale for the loading modes chosen (axial, bending, torsional, shear, etc.)
- the results, including the failure modes
- a discussion of the results in terms of the expected *in vivo* and clinical performance of the system (with reference to expected physiological loads with supporting literature)

Unless an adequate rationale is provided, all testing should involve a worst case construct design of the total system and not testing of individual components. When there are differences between the proposed system and the system tested, an explanation of how or

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Cunningham BW, Orbegoso CM, Dmitriev AE, Hallab NJ, Seftor JC, and PC McAfee. The effect of titanium particulate on development and maintenance of a posterolateral spinal arthrodesis: an *in vivo* rabbit model. *Spine* 15: 1971-1981, 2002.

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why the results are relevant in establishing the relative safety of the proposed system should be provided.

The test environment is dependent on the type of mechanical test being conducted. Some tests are done under ambient conditions, while it may be necessary for other tests to be conducted in a simulated physiologic solution (e.g., dynamic and wear debris testing). Justification for the test environment should be provided.

Please note all testing should be well described and summarized with a clear, detailed rationale and justification that the testing and results are appropriate and clinically relevant.

Test standards are currently being developed by ASTM and ISO for static/dynamic characterization of total artificial discs, as well as wear assessment. Only one of these standards has been published at this time (ASTM Standard F2345-05: Standard Test Methods for Static and Dynamic Characterization of Spinal Artificial Discs). Although none are currently recognized by FDA, they may provide guidelines for appropriate testing methods.

Static and Dynamic Characterization - Static and dynamic mechanical testing of the device is recommended to fully characterize the device. For most disc replacement designs, axial compression and compression shear is recommended. Depending on the design of the device, additional testing may be necessary.

Static testing should involve a minimum of six samples of a worst case construct. The fatigue testing should involve a minimum of six samples of the worst case construct to generate an Applied Force vs. Number of Cycles (AF/N) curve. At least two samples should survive ten million cycles at a specific load. The frequency of the dynamic testing, if it exceeds expected physiologic frequencies (1-2 Hz) should be justified in terms of its effects on the device materials (especially if it includes viscoelastic materials such as UHMWPE), test environment and temperature, and machine accuracy.

The compression-shear testing should be conducted using the device's maximum theoretical range of motion (ROM) in one or more of the directions of motion (full flexion/extension, full lateral bending, etc.). Justification should be provided for not testing any of these directions.

Many disc replacement devices are unconstrained in rotation, and therefore, torsional testing may not be applicable. Nonetheless, a rationale for not providing torsional testing should be included.

Durability/Wear - The theoretical ROM for the device in the various directions of motion (i.e., flexion, extension, lateral bending, axial rotation) should first be described to adequately characterize the device, and information should be provided to describe the method through which the ROM of the device was determined.

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The objective of the durability testing is to establish wear generation potential for the device as well as to possibly assess the stability. The durability/wear testing should involve cyclic loading that incorporates the various directions of motion. This test should be combined to incorporate all testing directions into one test, or separated into one or more motion directions. Because most devices will be subjected to coupled motions (simultaneous motion about multiple axes) *in vivo*, coupling at least two of the motions during the test is recommended. Each test specimen, regardless of test method used, should be subjected to ten million cycles in all directions. If one or more motions are being tested separately, the order of the motions should be varied among different specimens to determine if there is any effect by the order of testing.

Because different areas of the spine have different ROMs, the parameters for the durability testing will depend on the locations for which the device is intended (i.e., cervical or lumbar). The table below outlines test parameters that are currently recommended for cervical and lumbar disc replacements. These parameters have been chosen based on careful evaluation of the literature and testing that has been done and reported for various total artificial discs. If alternative parameters are chosen, sufficient justification should be provided which may include evaluation of the device in simulated motion studies in cadaver spines. Because the motion of the device can depend on the level of implantation and the test methods employed, sufficient justification should be provided to demonstrate that results from cadaver testing represent worst case ranges of motion for the device.

<b>Spinal Region</b>	<b>Flexion/Extension (degrees)</b>	<b>Lateral Bending (degrees)</b>	<b>Axial Rotation (degrees)</b>	<b>Frequency (Hz)</b>	<b>Test Duration</b>	<b>Preload (N)</b>
Cervical	±7.5	±6	±6	≤2	10 million cycles	100
Lumbar	±7.5	±6	±3	≤2		1200

All testing should be performed in a physiological solution (e.g., bovine calf serum) and the wear debris extracted from solution using appropriate method. For example, wear debris can be filtered through an appropriate sized filter with a pore size that allows collection of sub-micron particles. A complete description of the debris extraction and/or filtering procedure should be provided. The wear debris should be characterized in terms of size distribution, shape, and chemical composition and saved in case future analysis is necessary. The methods described in ASTM F561 and ASTM F1877 may be helpful in collecting and characterizing these particles.

We expect wear debris to be collected and characterized at least once every million cycles to determine if wear is increasing, decreasing, or remaining the same.

Some disc replacement devices are constrained (i.e., have limited range of motion) and alternative testing may be needed to evaluate the device out to the extreme angles. This testing should demonstrate that the device does not break down when it reaches the extreme angles and that excessive wear debris is not generated when the device reaches these extremes.

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Depending on the amount of clinical and animal data for the device, durability/wear testing may not be necessary at the time of IDE submission, and it may be possible to perform this testing concurrent with the clinical study with reporting of the results in the annual reports and/or at the time of PMA.

Subluxation/Expulsion - Adequate testing and justification should be provided to assess the risk of subluxation of the superior/inferior components and/or the disc spacer. The device should be tested in shear (or compression-shear) to expected *in vivo* loads taking into consideration an appropriate factor of safety. Depending on the design of the device it may be necessary to evaluate the risk of subluxation/expulsion in more than one loading direction.

Creep and Stress Relaxation - Because many disc replacement devices include viscoelastic materials that may be subject to creep and stress relaxation, appropriate testing and justification should be provided to assess this behavior. Creep testing under continuous compressive loading should be assessed on the final, sterilized device to demonstrate that the disc height can be maintained over the life of the implant with an accompanying hysteresis analysis.

Subsidence – The risk of subsidence of device components into the vertebral bodies should be addressed through appropriate testing and/or justification.

Kinematic Testing - A cadaver study evaluating the range of motion of the device *in vivo* compared to a normal spine is recommended. This study should use a justified number of samples to demonstrate consistent results.

Device Migration - Many disc replacement devices rely on press-fitting, ligamentotaxis, and rapid bony ingrowth into the endplates of the device to achieve adequate fixation. Sufficient justification and testing should be provided to establish that the risk of device migration is minimal. This would typically involve appropriate testing in an *in vivo* animal model to demonstrate that the surfaces of the endplates allow for rapid bone ingrowth and adequate fixation. Complete test reports including histology, characterization of ingrowth, time to achieve ingrowth, justification of the testing model, etc. should be provided.

Durability of Coatings - Adequate testing and justification should be provided to characterize the stability/durability of any coatings (e.g., shear, tension, abrasion, etc.). A complete and detailed description of the manufacturing process and chemical formulae of the coatings should be included. Testing should include an evaluation of the device and/or coatings under expected *in vivo* conditions to demonstrate that the coatings do not shear off. Methods described in ASTM F1044, F1147, F1160 and F1978 may be appropriate for these tests. Additional information should be provided to describe any potential *in vivo* by products. The following questions may be applicable if the coating is not permanent: How is the coating being dissolved? What type of reaction is there, if any? Does the coating cause any damage to surrounding tissue when it dissolves? Note that testing in a functional animal model with appropriate histological analysis may provide the best characterization and evaluation of the coating.

#### **4. BIOCOMPATIBILITY DATA**

General biocompatibility testing may be necessary based on the material(s) used to comprise the system. AAMI/ANSI/ISO 10993-1 is a recognized standard that can be referenced for a description of the type of information that should be provided to address biocompatibility. Please refer to the FDA-Blue Book Guidance for Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices, May 1, 1995 (G95-1) at the following web site for additional information: <http://www.fda.gov/cdrh/g951.html>.

In addition, animal data describing the response to the device material(s) in the spine may be necessary (see Animal Data section).

ASTM and ISO biocompatibility testing standards are based on contact with blood, not contact with neural tissue or cerebrospinal fluid (CSF). Therefore, if the system or any component of the system is manufactured from any other polymer (e.g., ultra high molecular weight polyethylene or UHMWPE, PEEK, PEKK, carbon-fiber PEEK, other composite polymer, etc), a characterization of the material (e.g., Stage I data for UHMWPE, leachables, material properties, molecular weight, molecular weight distribution, chemical and crystal structures, percent of crystallinity, the degree of cross-linking of that polymer) should be provided for both the raw material and the final sterilized material. In addition, a summary of the material processing and any solvents used throughout the manufacturing of the device should be provided.

For any materials manufactured from polymers or that have the potential for leachables, an exhausted extraction analysis of the final sterilized device should be performed. Extractions should be done using both a polar (e.g., saline) and a non-polar solvent (e.g., hexane, acetonitrile). Some solvents may be appropriate for certain materials, a rationale should be provided for the solvents chosen for the extraction tests. The test report should include, but is not be limited to, the instrument sensitivities, type of solvent used, the amount leachables and impurities detected at part-per-billion (ppb) levels, etc. Identify each leachable and impurity that is detected qualitatively and quantitatively, including the low molecular weight PEEK material, residual monomers, solvent, sulfur contents, catalysts, initiators, lubricants, etc.

#### **5. SHELF LIFE DATA**

We recommend that you evaluate all devices that can be affected by shelf life, sterilization, or aging (i.e., polymers). You should characterize the material of the final, sterilized device before and after aging to see if aging altered the material structure (e.g., molecular weight distribution, crystallinity, cross-linking, etc.) and/or the mechanical properties of the device. If shelf life or aging affects the component's material, then the same mechanical testing of that component or system should be performed before and after aging.

## **C. CLINICAL INVESTIGATIONAL PLAN**

The clinical study should be designed and conducted in a manner such that it provides data that will constitute valid scientific evidence within the meaning of 21 CFR 860.7. For guidance regarding clinical data presentation formats, please refer to “Clinical Data Presentations for Orthopedic Device Applications” (<http://www.fda.gov/cdrh/ode/guidance/1542.html>), issued on December 2, 2004.

Much of the information provided in the Guidance Document for the Preparation of IDEs for Spinal Systems (<http://www.fda.gov/cdrh/ode/87.html>) is directly applicable to IDEs for total artificial discs. For the sake of brevity, only information specific to total artificial discs and newly updated sections are presented in this “points to consider” document.

### **1. CHOOSING A CLINICAL INVESTIGATION PLAN: FEASIBILITY/PILOT VS. PIVOTAL STUDY**

Unlike IDEs for most orthopedic implants, IDEs for total artificial discs often involve the introduction of new device designs and investigational protocols. Therefore, protocols for total artificial discs may vary in scope from a feasibility/pilot study to a pivotal study used to support the safety and effectiveness of the device. These various types of studies are intended to address different questions and collect different types and amounts of safety and effectiveness information.

Please refer to Item 1. in the Investigational Plan section of the “Guidance Document for the Preparation of IDEs for Spinal Systems” (<http://www.fda.gov/cdrh/ode/87.html>) for full details.

### **2. PURPOSE / OBJECTIVE STATEMENT**

The clinical protocol should begin with clearly defined objective(s) and hypothesis(es).

Please refer to Item 2. in the Investigational Plan section of the “Guidance Document for the Preparation of IDEs for Spinal Systems” (<http://www.fda.gov/cdrh/ode/87.html>) for full details.

### **3. STUDY DESIGN**

The ideal and preferred vehicle for establishing safety and effectiveness for any device is the randomized clinical trial. However, FDA’s regulations implementing section 513(a)(3) of the Act establish a hierarchy of valid scientific evidence. Under 21 CFR 860.7(c)(2), endorsed by the US Preventive Services Task Force, quality of evidence (USPSTF–HHS) includes

- well-controlled investigations,
- partially controlled studies,
- studies and objective trials without matched controls,
- well documented case histories, and

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- reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its condition of use. Due to the potential for a placebo effect reported for novel interventional products used for treatment of pain, use of a randomized, concurrent **control group** is desirable to show safety and effectiveness of your spinal device. (ref: James G. Wright, Marc F. Swiontkowski, and James D. Heckman. "Introducing Levels of Evidence to *The Journal*" Journal of Bone Joint Surgery Am 2003 85: 1-3; CFR 21 860.7) This study design offers the benefits of prospectively acquired data, and, therefore, allows for tighter control of all parameters to be evaluated. The use of randomized concurrently controlled studies provides many advantages over other types of study designs by offering a tight control of all parameters and by addressing some of the biases introduced by the other study designs and is preferred in most instances.

Randomized concurrently controlled studies, non-randomized concurrently controlled studies, or historical-based studies may be proposed so long as the study design choice effectively addresses the safety and effectiveness of the spinal system and the inherent biases. Because these devices are novel and not currently in wide usage, FDA currently does not believe the use of objective performance criteria for clinical outcomes is appropriate for these types of device applications. Regardless of the type of control to be incorporated into the protocol, a complete description of the investigational and control groups should be provided. You should also provide a rationale for the proposed study design, based on established scientifically sound clinical and statistical principles, including how inherent biases are to be addressed with adequate additional support that the design proposed is justified.

Please refer to Item 3. in the Investigational Plan section of the "Guidance Document for the Preparation of IDEs for Spinal Systems" (<http://www.fda.gov/cdrh/ode/87.html>) for full details.

## **4. CHOICE OF CONTROL**

Regardless of the type of control to be incorporated into the protocol, a complete description of the investigational and control groups should be provided. The sponsor should also provide a rationale for the proposed study design, including how inherent biases are to be addressed.

Please refer to Items 3.1 and 3.2 in the Investigational Plan section of the "Guidance Document for the Preparation of IDEs for Spinal Systems" (<http://www.fda.gov/cdrh/ode/87.html>) for full details about the different choices of controls.

Please note that pooling of patients into a single control cohort from published studies should be justified. A true meta-analysis is statistically complicated and is not simply a result of adding together multiple groups of patient populations to provide a cohort. We encourage

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you to consult with FDA staff to assist in providing adequate information to justify a literature control.

### **5. INCLUSION CRITERIA**

Complete inclusion criteria are essential to adequately define the patient group to be investigated. The criteria for inclusion into any clinical study of a total artificial disc will differ depending on the disease population targeted for the proposed treatment and the location of the disease process (i.e., cervical, thoracic, lumbar). Please refer to Item 4. in the Investigational Plan section of the “Guidance Document for the Preparation of IDEs for Spinal Systems” (<http://www.fda.gov/cdrh/ode/87.html>) for full details.

In addition to the inclusion criteria listed in the Spinal Systems guidance document, the following additional criteria should be considered for total artificial disc studies:

- description of any restrictions regarding prior fusion, non-fusion or adjacent level surgeries
- description of the status of the adjacent spinal levels both radiographically and clinically (facet degeneration, disc height, osteophytes, etc.)
- scoliosis of less than 5 degrees
- conditions of minimum bone density or quality for bony ingrowth or fixation
- condition of instability or presence of stability defined by accepted parameters

Because of the inherent instability of the spine that may occur from the resection of primary or metastatic tumors, the use of some non-fusion spinal systems may not be appropriate in patients with spinal tumors. Information specific to tumors metastatic to the spine is described in detail in Section 17 below.

Studies involving patients with more than one level requiring fusion have typically demonstrated poorer outcomes than patients with single level treatment. Since little is known about the treatment of multiple levels with motion sparing devices, if you would like to include evaluation of use of your device at two or more levels, a statistically significant sample size and clinical justification should be provided and the results stratified separately from those for single level patient outcomes. FDA suggests that patients be limited to those with disease confined to one or two adjacent levels for study consistency.

The next sections address specific disease processes and anatomic spinal regions individually.

#### ***Degenerative Disc Disease (DDD)***

Please refer to Items 4.1 (lumbar DDD) 4.6 (cervical DDD) in the Investigational Plan section of the “Guidance Document for the Preparation of IDEs for Spinal Systems” (<http://www.fda.gov/cdrh/ode/87.html>) for full details.

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### ***Scoliosis***

Currently, diagnosis of pediatric congenital and adolescent scoliosis may be considered contraindications for total artificial discs. Axial, translational and rotational forces of the spine in these patient populations may lead to early failure of these types of devices. Please refer to Item 4.2 in the Investigational Plan section of the “Guidance Document for the Preparation of IDEs for Spinal Systems” (<http://www.fda.gov/cdrh/ode/87.html>) for full details.

### ***Fractures Secondary to Trauma***

Principles of acute fracture treatment contradict allowing immediate motion if fracture healing is desired. Adequate justification for safe use of total artificial discs for this indication should be provided. Please refer to Item 4.3 in the Investigational Plan section of the “Guidance Document for the Preparation of IDEs for Spinal Systems” (<http://www.fda.gov/cdrh/ode/87.html>) for full details.

### ***Spondylolisthesis***

FDA does not believe that patients with moderate to severe cases of spondylolisthesis and/or instability are appropriate candidates for total artificial discs. You should provide adequate justification that your device is safe for the treatment of mild spondylolisthesis. Please refer to Item 4.4 in the Investigational Plan section of the “Guidance Document for the Preparation of IDEs for Spinal Systems” (<http://www.fda.gov/cdrh/ode/87.html>) for full details.

### ***Revision Surgery for Pseudoarthrosis***

FDA believes that total artificial discs may be contraindicated for revision surgery for failed fusions.

## **6. EXCLUSION CRITERIA**

Complete exclusion criteria are essential in adequately defining the patient group to be investigated. This is because exclusion criteria may address a safety concern associated with a specific type of patient and/or allow for the exclusion of patients who may negatively impact the study results and data analyses. Please refer to Item 5. in the Investigational Plan section of the “Guidance Document for the Preparation of IDEs for Spinal Systems” (<http://www.fda.gov/cdrh/ode/87.html>) for full details.

In addition to the exclusion criteria listed in the Spinal Systems guidance document, the following additional criteria should be considered for total artificial disc studies:

Safety concerns:

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- identifying a remaining disc space of 5-7 mm is recommended, excluding patients with less than 5 mm of disc space remaining (This criterion may be modified based on the particular intended use or mechanics of your device.)
- subject has an additional spinal condition other than the condition to be studied which may increase symptoms with additional motion or preclude insertion of the device (These conditions should be clearly defined and listed specifically.)
- subject is on chronic medication affecting bone metabolism (steroids, osteoclast inhibitors, etc.)
- congenital stenosis, or central/lateral stenosis secondary to acquired degenerative disease requiring treatment that destabilizes the spine (requiring fusion), or for patients in whom increased motion may increase symptoms
- myelopathy (if included, should be justified by device design and include stratification of diagnostic groups)
- severe spondylolisthesis of greater than 3mm (> Grade I)
- subject has severe degenerative disease, including facet degenerative arthrosis and adjacent level degeneration which precludes safe implantation of the device without significant destabilization of any portion of the spinal column or due to anatomic deformity This includes any procedure which will leave the patient with deficient postoperative deficiency of the posterior elements, or in any case , for example with facet arthroplasty devices, postoperative instability of the middle or anterior columns.
- subject has spinal deformity, instability, scoliosis or kyphosis which precludes safe use or surgical intervention. The range of excluded radiographic measurements or clinical symptoms should be clearly and specifically defined.

#### Follow-up concerns:

- subject is referred from a location that is greater than 150 miles from the investigational site

#### Those that simplify/clarify study design:

- subject has multiple involved levels in the spine
- subject had prior surgery at the proposed surgical level (Adequate justification for pooling subjects who have never had surgery with those who have had one or more prior incisions should be justified.)

## **7. NUMBER OF SITES/INVESTIGATORS/PATIENTS**

The proposed number of investigators, investigational sites, and patients should be specified. Please refer to Item 6. in the Investigational Plan section of the “Guidance Document for the Preparation of IDEs for Spinal Systems” (<http://www.fda.gov/cdrh/ode/87.html>) for full details.

## **8. DURATION/FOLLOW-UP SCHEDULE**

In order to properly assess all safety and primary effectiveness outcomes, your study should involve a minimum of 2 years of follow-up data. However, you may propose a shorter study with an adequate rationale. Please refer to Item 7. in the Investigational Plan section of the “Guidance Document for the Preparation of IDEs for Spinal Systems” (<http://www.fda.gov/cdrh/ode/87.html>) for full details.

Because novel spinal devices are being developed to address spinal disorders in younger, more active populations, you should also be prepared at the time of IDE submission to address the possibility of plans for post approval studies, which follow a statistically and clinically significant sample of patients for safety and effectiveness for 5-10 years after implantation.

## **9. EFFECTIVENESS EVALUATION**

There are primary and secondary evaluation parameters for all total artificial disc studies that should be measured at each timepoint. The specific parameter scales and methods of interpretation (success/failure criteria) with rationale/validation should be included. Please refer to Item 8. in the Investigational Plan section of the “Guidance Document for the Preparation of IDEs for Spinal Systems” (<http://www.fda.gov/cdrh/ode/87.html>) for full details.

Recommended endpoints for total artificial disc studies are discussed below.

For lumbar spinal studies, primary evaluation parameters should include at a minimum:

- *back and/or leg pain; and*
- *patient activities of daily living (ADL) function*

For cervical spinal studies, primary evaluation parameters should include

- *neck and arm pain; and*
- *patient activities of daily living (ADL) function*

Clinical and radiographic absence of device migration/failure, absence of fusion, and presence and amount of motion should be evaluated and documented for any spinal level treated and the adjacent “normal” spinal levels. Depending on the design of your device, bone ingrowth or adequacy/stability of fixation or other applicable parameters may also be study endpoints that are evaluated.

The choice of the following parameters as primary or secondary depends on the intended use and claims for your device, but should be included in the investigational study:

- neurologic status (should be evaluated at each time point)
- disc height/vertebral height maintenance assessment

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- range of motion at the treated level
- health-related quality of life
- patient satisfaction
- return to work status.

The success criteria for each of the individual primary evaluation parameters will differ based upon the design of the system, the patient population, and the goals of the treatment. Recommended endpoints are discussed in detail below.

### 9.1 Radiographic Success

For total artificial discs, the radiological assessments depend on the patient population and study goals. These assessments may include integrity of implant, maintenance of correction and/or stability, lack of migration, and/or maintenance/amount of motion.

Radiographic evaluation should provide both safety information and efficacy information about the investigational device. In order for radiographic evaluation to provide useful information, it is important that investigators and independent radiologists identify successfully placed devices and those that are not in the proper location or have moved from their original position.

Please refer to Item 8.1 in the Investigational Plan section of the “Guidance Document for the Preparation of IDEs for Spinal Systems” (<http://www.fda.gov/cdrh/ode/87.html>) for full details.

#### 9.1.1 Radiographic Safety Success

Devices which allow motion should provide evidence that the operative level and adjacent levels are stable and do not allow slippage in any direction *in situ*. The degree of motion in this case should be documented in each plane of potential motion for the operative and adjacent levels.

There are two distinct purposes for radiographic evaluation of implant location. First, the investigator should determine whether the implant was successfully placed in the intended location. This should be documented at the time of surgery or immediately after the procedure. Second, the evaluation should clearly define the position of the device in relation to the initial implantation location, as well as the ideally desired location. For example, a radiographic report should include the position relative to the initial implantation, the position relative to the desired location, and the position during flexion/ extension films. Both indicate similar motion during activities of daily living and of safety concern and should be documented during radiographic evaluation.

In addition to the above measurements, radiographic evaluation of the adjacent segment degeneration and general status should be reported.

Evidence of stable implant fixation and/or bone ingrowth area, depending on the design of the device, should be in excess of 75% of the bone/implant surface intended for ingrowth.

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### 9.1.2 Radiographic Efficacy Success

Devices intended to maintain motion should document maintained or improved motion. Radiographic motion as determined from flexion/extension plain radiographs, MRIs or other specialized radiographic methods should be able to estimate both preservation of motion at both the operative and at the adjacent levels.

Efficacy endpoints that should be demonstrated include:

- successful preservation or improvement of motion ( rotational, flexion/extension, lateral bending, translational, and/or angular) based on:
  - the physiologic requirements of the anatomic level(s) and levels adjacent to the level(s) being treated
  - the preoperative motion at the treated level(s)
- absence of evidence of bridging trabecular bone between the involved motion segments
- correlation between motion and clinical symptoms should be included in analysis

For two-level involvement, both levels should maintain motion to be considered a success.

### 9.2 Pain and Function

Please refer to Item 8.2 in the Investigational Plan section of the “Guidance Document for the Preparation of IDEs for Spinal Systems” (<http://www.fda.gov/cdrh/ode/87.html>) for full details.

The patients’ severity and frequency of pain should be assessed both pre- and postoperatively at specific follow-up times. Attempts need to be made to distinguish pain due to problems with the spine, e.g., nerve root impingement, from the general pain that these patients might experience as the result of their overall medical condition, both at enrollment and post operatively. Consideration should also be given to the type of analgesic medication the patient is using and how that may affect the pain assessment score.

Evaluation of function should focus on the ability of patients to function independently, e.g., how does their ability to better move around the house/neighborhood, dress themselves, etc. compare to their pre-op status, but may also include depending on the population studied return to recreational activities. Return to work is also a parameter of interest in the working population.

Success criteria for pain and function improvement should take into consideration the potential for a placebo effect (between 20-30%) and adjust the degree of improvement accordingly (typically greater than 25-30% as compared to preoperative status). The FDA believes that a consistent numerical value (such as 15/50 on the ODI) for each patient be used for success determinations for subjective assessment scales. The clinically meaningful level of improvement, which may be different than the statistical level of improvement, should be clearly specified.

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### 9.3 Disc and Vertebral Height Assessment

Please refer to Item 8.3 in the Investigational Plan section of the “Guidance Document for the Preparation of IDEs for Spinal Systems” (<http://www.fda.gov/cdrh/ode/87.html>) for full details.

Disc heights adjacent to the operative level should also be measured and followed over time, but do not necessarily require success criteria for the study, depending on the intended use and claims for your device.

### 9.4 Health Related Quality of Life

Please refer to Item 8.4 in the Investigational Plan section of the “Guidance Document for the Preparation of IDEs for Spinal Systems” (<http://www.fda.gov/cdrh/ode/87.html>) for full details.

## **10. SAFETY EVALUATION**

Please refer to Item 9. in the Investigational Plan section of the “Guidance Document for the Preparation of IDEs for Spinal Systems” (<http://www.fda.gov/cdrh/ode/87.html>) for full details.

Any subsequent procedures related to the index level should be reported and categorized as a supplemental fixation. This would include posterior fusion, leaving or removing the device in place, decompression, facet rhizotomy, etc. at the same, adjacent or distant levels. Other surgical interventions should be reported separately.

Signs of myelopathy and gait disturbances should also be included where applicable, particularly for cervical implant investigations.

Cervical tension signs (Spurling’s sign) and gait analysis may be appropriate for cervical implants that allow semi-constrained or unconstrained range of motion.

### **Metal Ion Release**

Published information for use of hip implants using metal-metal articulating surfaces has raised safety concerns (e.g., the risk of tumor formation, carcinogenesis potential in human patients). Although retrieval analyses may be able to address some safety issues regarding metal-on-metal wear debris, FDA does not believe that the issue of metal ion release has adequately been investigated in the spine. FDA believes that all investigational protocols for metal-on-metal articulating devices intended to maintain motion in the any part of the human spine include, at a minimum, serum ion level studies during investigation of the safety and effectiveness of the device for its intended use. Please refer to the recommendations published in the Metal on Metal Total Hip Replacement Workshop Consensus Document (Amstutz, HC, et al. Clinical Orthopaedics and Related Research, No. 329S, 1996, S297-S303) to evaluate metal ion release levels in patients with metal-on-metal total artificial discs. Your investigation should include an evaluation addressing the potential for the risk of tumor formation and/or carcinogenesis potential in human patients or provide a rationale

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with supporting references that indicate that either additional safety testing is not needed or that these risks have been adequately addressed in your preclinical testing.

### **11. PATIENT/STUDY SUCCESS**

Patient success may include a combination of objective and subjective criteria. Consideration of the placebo effect (typically 20-30%) should be taken into account when determining the amount of clinically significant improvement that constitutes patient success in subjective patient-administered assessment scales.

The success of a patient should be based, at a minimum, on success in each of the primary evaluation parameters of pain and function, as well as no permanent neurological deficit, absence of secondary surgical intervention, and absence of serious adverse events. Depending on the proposed patient population, study design, and study goals, other assessments may be included. Patients who undergo certain secondary surgical interventions or experience serious adverse events or neurological deficits are considered failures of treatment. Improvement in pain and function should indicate clinically significant benefit, such as improvement of at least one subjective severity category to justify the risks of surgery (such as marked to moderate disability, or severe to moderate or mild pain). Depending on the particular goals of your investigation, justification for other benefits over the anticipated risks may be made. This determination may be also based on the minimum severity levels required as entry criteria in the inclusion criteria for your study or the patient's baseline status/scores on the patient administered assessment scales.

Please refer to Item 10. in the Investigational Plan section of the “Guidance Document for the Preparation of IDEs for Spinal Systems” (<http://www.fda.gov/cdrh/ode/87.html>) for full details.

### **12. STATISTICAL ANALYSES/DATA PRESENTATIONS**

It is very important that the type of analysis (Bayesian or traditional/frequentist) be chosen before the study commences. Both Bayesian and frequentist statistical methods of analysis may be used. For more information on each of these methods, please refer to <http://www.fda.gov/cder/Offices/Biostatistics/guidances.htm>.

Switching methods makes it necessary to justify and to model the reasons the switch was made in order to avoid possible biases.

Please note that FDA recommends that statistical methods such as Bayesian statistics may be used to account for missing effectiveness data, but not for safety information. You should be advised that statistical methods are not an adequate substitute for completing your study and should not be used as a substitute for following patients at a minimum through the entire study or for ending the IDE prematurely. Statistical plans to account for or adjust for missing data should be provided at the IDE stage.

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Subgroup analyses may help you and FDA better understand the behavior of the subpopulations for which the device is indicated. Thus, at the time of PMA, FDA may request further subgroup analyses to assess the safety and effectiveness data of the investigational device in these subpopulations.

The types of data presentations should be considered at the time of protocol development in order to better assure that adequate data are collected. In order to properly evaluate the data, it is imperative that you clearly identify the number of patients involved at a given time point in any data presentation. For complete details on the preferred formats for clinical data presentation please refer to the “Clinical Data Presentations for Orthopedic Device Applications” (<http://www.fda.gov/cdrh/ode/guidance/1542.html>).

Please refer to Item 11 in the Investigational Plan section of the “Guidance Document for the Preparation of IDEs for Spinal Systems” (<http://www.fda.gov/cdrh/ode/87.html>) for full details.

## **13. PATIENT REPORT FORMS**

Copies of all patient report forms should be provided. The forms should report all relevant information from the protocol. Depending on the intent of the study more case report forms (CRFs) may be needed. Note that original source documents (such as doctor’s office notes, operative notes, radiographs or patient self-assessment questionnaires) should be consistent with and reflect the data recorded on these case report forms.

In addition to the types of case report forms listed in the Spinal Systems guidance document, the following additional items should be considered for total artificial disc studies:

- Operative Data form should document implant type, size, and number used, as well as any intraoperative observations or adverse events
- Adverse Event form - identifies all potential risks from the protocol and provides for reporting of other adverse events, device related or not, spaces for the date, action taken and date of resolution of the event should be included. Where applicable, the severity and association of the event to the device or procedure should be included in the documentation
- Copies of each of the clinical evaluation scales or assessment questionnaires should be included (VAS, Oswestry Disability Index, SF-36, patient satisfaction, work status, etc.)
- A separate CRF for the independent radiographic review should be included
- Study Exit form - documents patient’s exit from the study population due to study completion, withdrawal or loss to follow up
- Special testing report form - such as blood metal ion results

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Copies of each of these case report forms should be provided for each evaluation interval as appropriate in the investigator's protocol package for each enrolled patient.

Please refer to Items 12. in the Investigational Plan section of the "Guidance Document for the Preparation of IDEs for Spinal Systems" (<http://www.fda.gov/cdrh/ode/87.html>) for full details.

When using computerized or internet-based patient assessment forms, please follow the guidelines outlined in "Computerized Systems Used in Clinical Trials" ([http://www.fda.gov/ora/compliance\\_ref/bimo/ffinalcct.htm](http://www.fda.gov/ora/compliance_ref/bimo/ffinalcct.htm)). Please be advised that in the event of an inspection or audit, FDA may request access to source documents of collected data.

## **14. RISK ANALYSIS**

This section should include adequate information to determine that the benefits and knowledge to be gained outweigh the risks to the patients. When listing all of the potential risks, they should be stratified by those general to spinal surgery and those specific to the device. Please refer to Items 13. in the Investigational Plan section of the "Guidance Document for the Preparation of IDEs for Spinal Systems" (<http://www.fda.gov/cdrh/ode/87.html>) for full details.

Examples of device complications include, but are not limited to:

- Loss of function
- Fracture, subluxation, subsidence, or dislocation of the device.
- Fracture of the adjacent bony structures
- Heterotopic Ossification or segmental fusion (as relates to loss of motion)
- Excessive wear, migration, of the device or any of its components, even if such failure does not lead immediately to revision surgery or symptoms.
- Facet degeneration at same level
- Adjacent Segment degeneration
- Adjacent disc degeneration or intravertebral space height loss
- Infection at the level of the device
- Neurovascular compromise secondary to device impingement of these structures
- Toxicity, carcinogenic potential or other biologic local or distant tissue or systemic effects due to by-products, debris (metal ion release) or breakdown products related to the device functioning in situ under physiologic conditions

Examples of surgery in general and surgical approach complications include, but are not limited to:

- Neurological complications, temporary and permanent
- Vascular injury
- Sympathetic disturbance
- Painful or numb scar
- Hematoma

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- local drainage
- New pain or pain progression
- Retrograde ejaculation
- Dysphagia
- Hoarseness/vocal cord dysfunction
- Abdominal adhesions

Examples of complications considered general complications of surgery include, but are not limited to:

- Visceral dysfunction
- Abdominal pain
- disturbance of urinary function
- Urinary tract infection
- Deep vein thrombosis
- Phlebitis
- Pulmonary embolism
- Myocardial Infarction
- Cerebrovascular Accident
- Death

## **15. POST-OPERATIVE REGIMEN**

Any additional patient care procedures to be employed during the treatment period (e.g., surgery, rehabilitation, immobilization, weight bearing, etc.) should be detailed.

## **16. RETRIEVAL STUDY**

Because of the unknown long term device performance of some types of total artificial discs, a sponsor should incorporate a plan that focuses on the retrieval analyses of the total artificial disc that is implanted and subsequently removed. Please refer to Items 15. in the Investigational Plan section of the “Guidance Document for the Preparation of IDEs for Spinal Systems” (<http://www.fda.gov/cdrh/ode/87.html>) for full details.

In addition to the retrieval study recommendations presented in the Spinal Systems Guidance, a biopsy, (within the limits of safety) of surrounding bony and soft (neurovascular) tissue should be analyzed for inflammatory or other reaction to implants, and, where appropriate, metal ion or material debris content in surrounding tissue.

Specific instructions for the handling and return of explanted devices should be provided in the protocol, labeling and surgical technique. This aspect of the investigation should be part of the investigator training.

## **17. SPINAL TUMORS**

Devices which maintain motion may not be appropriate for use in patients with primary or metastatic neoplastic disease, due to the disease processes and adjunctive treatments which affect bone quality, spinal stability and patient longevity. You should justify the use of a motion retaining device in patients with spinal neoplastic disease. Please refer to Item 16. in the Investigational Plan section of the “Guidance Document for the Preparation of IDEs for Spinal Systems” (<http://www.fda.gov/cdrh/ode/guidance/87.html>) for devices to stabilize the spine when treating spinal tumors.

## **D. MONITORING**

The following is not information specific to a total artificial disc IDE but is necessary to complete the IDE submission:

- (1) a copy of the written procedures for monitoring the investigation. These procedures should meet the minimum requirements described in 21 CFR 812.46; and
- (2) the name and address of the monitor.

Please refer to the Monitoring section of the “Guidance Document for the Preparation of IDEs for Spinal Systems” (<http://www.fda.gov/cdrh/ode/87.html>) for full details.

We recommend that you develop a comprehensive monitoring plan. Experience has shown that if you make adequate provisions for monitoring studies, the quality of the studies and data will follow. Therefore, we recommend:

- selecting qualified monitors
- ensuring investigator adherence to the investigational plan and other requirements
- ensuring investigator compliance in regard to record keeping and reporting.

## **E. LABELING**

In accordance with 21 CFR 812.20(b)(10), copies of all labeling for the system should be provided. Please refer to the Labeling section of the Guidance Document for the Preparation of IDEs for Spinal Systems (<http://www.fda.gov/cdrh/ode/87.html>) for full details.

In addition to the information presented in the Spinal System Guidance, the following items should be included in the surgical technique manual:

- The intended uses/indications, device description, contraindications, precautions, warnings, and potential risks associated with the subject system or a statement of reference to the product insert for this information should also be included. We recommend that specific instructions which affect the

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safety of use, or which are noted to be uncommon in current practice, be highlighted or bolded for emphasis.

- FDA recommends that you include information in the surgical technique manual for explanting the device and revising the original procedure, should it be necessary, and describe a salvage procedure alternative to revision or reimplantation, if circumstances require it.

## **F. INFORMED CONSENT**

In accordance with 21 CFR 812.20(b)(11), copies of all forms and informational materials to be provided to the subjects in order to obtain informed consent are to be provided. In addition, a statement that the subject must sign the informed consent document prior to entrance into the study should be provided.

The informed consent document is to meet the general requirements as described in 21 CFR 50.20. Please refer to the Informed Consent section of the Guidance Document for the Preparation of IDEs for Spinal Systems (<http://www.fda.gov/cdrh/ode/87.html>) for full details.