Musculoskeletal Clinical
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Nucleus Arthroplasty™
From the U.S. Regulatory Viewpoint

Creating Value Throughout the Device Approval Continuum

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Nucleus Arthroplasty™ from the U.S. Regulatory Viewpoint

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REGULATORY OVERVIEW

At the current time, the Food and Drug Administration (FDA) considers the term nucleus arthroplasty as broadly applicable to any device that replaces the nucleus pulposus while preserving the surrounding annulus. Such devices are intended to reduce pain and increase function without fusing the spine. The key features of the FDA's definition include:

- Device location (i.e., placement in the nucleus space)
- General intent of the device (i.e., not intended to fuse the spine)

Although devices may be varied in their designs, materials, technological characteristics, and implantation methods, any device that meets the basic criteria outlined above will be regarded by the FDA as a nucleus arthroplasty system.

The regulatory pathway for marketing approval of nucleus arthroplasty devices involves a Premarket Application (PMA) submission to the FDA. A PMA should establish reasonable assurance of safety and effectiveness for a novel therapy or device, typically using valid scientific evidence that is collected in a well-controlled clinical trial. FDA approval for an Investigational Device Exemption (IDE) will allow unapproved devices to be studied in a clinical trial to gather this data. Such trials are designed to measure patient pain and function at selected time points following implantation of the nucleus arthroplasty device. This data is most often compared to a control based on the current standard of care.

NUCLEUS ARTHROPLASTY TECHNOLOGIES – CURRENT U.S. IDE PILOT STUDIES			
COMPANY	TECHNOLOGY	INDICATION	APPROVAL DATE
1 Spine Wave, Inc.	NuCore™	Adjunct To Microdiscectomy	Feb-06
2 Raymedica, LLC	HydraFlex™	Not Publicly Available	Jun-06
3 Spine Wave, Inc.	NuCore™	Degenerative Disc Disease	Jun-06
4 Disc Dynamics, Inc.	DASCOR™	Not Publicly Available	Aug-06
5 Pioneer Surgical Technology	NUBAC™	Not Publicly Available	Aug-06

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Currently there are no FDA approved nucleus arthroplasty devices. As of August 2006, four companies are in the process of conducting five U.S. IDE pilot clinical trials of nucleus arthroplasty technologies.

Although nucleus arthroplasty devices may offer many benefits compared to the current standard of care, device design issues and clinical concerns must be addressed in order to gather the data necessary to demonstrate safety and effectiveness. These issues and concerns should be addressed by means of appropriately-designed pre-clinical and clinical studies.

CHALLENGES FOR MANUFACTURERS AND THE FDA

Even in the initial stages of development for new and innovative therapies, the FDA must require that the preliminary safety of the device be established prior to starting a human clinical trial. This represents a formidable obstacle for most device manufacturers because of limitations in testing and characterization methods. Often when dealing with novel technologies, industry standards and FDA guidance documents are not available to provide direction in regard to validation methods. In the case of nucleus arthroplasty devices, the variety of materials, designs, and surgical implantation techniques have made it virtually impossible to create standardized testing that could be applied to the diversity of devices. Creating tests that are clinically relevant is also challenging for the device manufacturer. Safety profiles may be very different for each device design; however, testing must be designed and conducted to demonstrate that devices will not cause unforeseen risks. The device's intended use should direct both pre-clinical and clinical evaluations, including material selection, device design, pre-clinical testing, surgical technique, and clinical study design. A clear understanding of the device's intended use will also facilitate regulatory negotiations, and will offer the FDA the opportunity to provide clear feedback during the pre-clinical and clinical study design stages.

In the face of all these challenges, it is important for the manufacturer to work diligently and consult with the FDA early in the process to develop appropriate pre-clinical testing. Ideally, this effort will yield results that are scientifically and clinically relevant, and that ultimately demonstrate the safety of the device.

REGULATORY REQUIREMENTS

Regulatory requirements for conducting clinical trials and subsequent PMA applications include extensive preliminary design validation and pre-clinical studies. The following are some of the many challenges involved:

- Identifying the appropriate patient population
- Selecting appropriate device materials
- Designing the optimal device and placement technique
- Planning and implementing pre-clinical testing
- Implementing the clinical trial

PATIENT POPULATION

Paramount to the development of new treatment alternatives is a clear understanding of the capabilities and success of available treatment options in contrast to the unmet patient needs. Within the confines of degenerative disc disease, the potential playing field seems to be exceptionally large as there is a significant gap between the conservative and surgical treatment options that are currently implemented to cover a wide range of indications and potential degenerative disease stages.

In general terms, nucleus arthroplasty technologies represent a host of potential products designed to address degenerative disc disease. Ideally, the shape, form, and function of each device will be tailored to meet the individual needs of the patient population at a specific stage within the degenerative disc cascade.

The success of any nucleus arthroplasty device will be directly tied to the ability of a particular technology to be properly matched to a defined patient indication. However, trying to identify the correct patient population and the appropriate time for surgical intervention are among the biggest clinical challenges facing those who study nucleus arthroplasty devices. From the regulatory perspective, device manufacturers will be challenged to both define the intended treatment population and establish evidence of improvement with the proposed device in relation to the current standard of care.

NUCLEUS ARTHROPLASTY DEVICES MAY OFFER A GOOD ALTERNATIVE TO TREAT INDICATIONS WHERE THERE IS NO RELIABLE OR EFFECTIVE STANDARD OF CARE.

DEVICE MATERIAL

Determining the appropriate material is one of the key issues involved in engineering nucleus arthroplasty devices, since inappropriate material selection can contribute to potential failure modes. Each material presents its own regulatory hurdles because of the lack of validated characterization methods. As material technologies have advanced, testing standards and characterization methods have remained relatively stagnant. Therefore, older or non-validated testing methods must be used which may pose risks to the patient if not performed adequately. While the FDA can provide valuable feedback about the potential risks and concerns associated with each device, appropriate material characterization activities (i.e., mechanical, animal, and material tests) must be determined by the manufacturer.

There are several options that can be used to describe and characterize the device material. General biocompatibility evaluation and testing as recommended in the ISO Standard 10993 is required and should be performed at the initial stages of material development. Animal testing is often required to further study the material. Ideally, animal testing can be performed in a functional model in which the device is implanted using similar methods to those intended for human use. Establishing a functional model that appropriately evaluates the device in an animal can be difficult due to the differences in spinal anatomy and biomechanics between humans and animals. In such instances where an appropriate functional evaluation cannot be performed, animal testing may be conducted in which the primary focus is to evaluate the effects of material particulate in potential worst-case wear debris conditions. The particulate test usually consists of implanting an appropriate and clinically relevant wear debris particle quantity, shape, and size distribution into the spine of a small animal, such as a rabbit. The intent of this test is to eliminate potential risks associated with the material.

DEVICE DESIGN

Obviously, the material and design elements of any nucleus arthroplasty device are intimately linked. The broad spectrum of available materials has resulted in many different nucleus arthroplasty device designs. The challenge is to determine the best device design for the intended patient treatment population. Each individual design will have specific implications in regard to indications, patient selection, surgical technique and post-operative rehabilitation.

Device design performance requirements will also be strongly influenced by the indications of the selected treatment population. As such, it is critical to completely define the design rationale for the device. This can prove to be a daunting task when working with nucleus arthroplasty technologies as the load environment could be greatly influenced by many factors such as the level of the disease, bone quality, placement of the device, and the degenerative disease stage. This situation is further exacerbated by the limited information and clinical experience available to use in defining appropriate design parameters. All of these factors can affect the clinical results, welfare of the patient, and ultimately, the success of a particular device.

EACH INDIVIDUAL DEVICE DESIGN WILL HAVE SPECIFIC IMPLICATIONS IN REGARD TO INDICATIONS, PATIENT SELECTION, SURGICAL TECHNIQUE AND POST-OPERATIVE REHABILITATION.

THE ABILITY TO USE TECHNOLOGICALLY ADVANCED MATERIALS, DESIGN PARAMETERS, SURGICAL APPROACHES, AND INSTRUMENTATION AFFORDED BY NUCLEUS ARTHROPLASTY CAN MINIMIZE THE RISKS ASSOCIATED WITH IMPLANTATION.

In addition to assessing the potential mechanical challenges imposed on the design, all potential factors associated with the surgical approach and device delivery method must also be scrutinized. The device may have an ideal design based on biomechanical factors, however, the surgical approach, surgical instruments, and overall surgical procedure may significantly affect patient outcomes.

PRE-CLINICAL TEST PLANNING AND IMPLEMENTATION

Preliminary data on nucleus arthroplasty devices can be gathered from various studies worldwide. However, most of these studies have not been long-term, prospectively defined, controlled, randomized, or powered with the sample size required to make a strong conclusion about the device being studied.

In order to adequately show the device design is safe, potential failure modes and clinical risks must be described and mitigated. Mechanical testing is generally used to evaluate device mechanics under clinically relevant and/or worst-case loads and displacements. The type of test that is required will vary depending on the particular device design and intent. A complete evaluation of the device in a biomechanical model such as a cadaver spine is important to understand the device mechanics and simulated anatomical performance. Such testing may also provide valuable information about the device, surgical approach, proposed surgical instruments, and surgical technique. Loading the spine in various scenarios may also provide insight into potential clinical failure modes. While many of these failure modes can be addressed mechanically, there may still be instances in which the device performs perfectly in a simulated setting yet shows significant failures in subsequent patient evaluations. While mechanical testing has significant value, comparison of the results to a clinically successful device or scenario is almost impossible.

CLINICAL TRIAL IMPLEMENTATION

After completing the appropriate pre-clinical testing to characterize device materials, validate the design, and gather preliminary safety data, a device manufacturer must provide all this information to the FDA. These results will be reviewed by the FDA and used to justify approval of the human clinical trial. The data collected in the trial will be used to demonstrate the safety and effectiveness of the therapy in the PMA application.

IDE PILOT

Since nucleus arthroplasty devices are still considered a novel therapy that utilize a wide array of designs, materials, and implantation techniques, the FDA will likely require a pilot study to ensure that these parameters have been optimized. This is especially true in cases when bench testing is not adequate to characterize device safety. The IDE pilot study, also known as a feasibility study, is a limited human clinical study designed to answer specific questions associated with the device or implantation method and to establish the preliminary safety of the device and surgical technique. The length of a pilot study can vary from six months to two years and is largely dependent on the questions or concerns that are being addressed. Specific concerns about device material, mechanics, or biological effects may require a study of longer duration while concerns associated with items such as the surgical technique may be relatively short. As indicated, a pilot study may assist in addressing concerns that cannot be tested on the bench. For example, published literature has reported device expulsions with certain nucleus arthroplasty device designs. However, this particular device failure mode did not occur during bench, biomechanical, or animal testing. Clearly, additional bench testing in such situations does not positively contribute to the existing knowledge base. Thus, small pilot studies are conducted to provide data that cannot be obtained strictly through pre-clinical testing.

PROPER SELECTION OF A CONTROL GROUP IS EXTREMELY IMPORTANT AS THE TREATMENT RESULTS FOR THE CONTROL WILL SERVE AS A BASIS FOR COMPARISON IN REGARD TO DEVICE SAFETY AND EFFECTIVENESS.

IDE PIVOTAL

After the pilot study has been completed and all questions or concerns regarding device safety have been addressed, the manufacturer must conduct a clinical study comparing the device to a valid control. The clinical trial design of the pilot study is often very similar to the IDE pivotal study. As discussed earlier, selecting a control group can prove to be very difficult in the case of nucleus arthroplasty devices. Proper selection of a control group is extremely important as the treatment results for the control will serve as a basis for comparison in regard to device safety and effectiveness. Selection of a control group that does not closely match the indications and intended patient population will make it difficult for the FDA and Centers for Medicare and Medicaid Services (CMS) to determine the clinical meaning behind the data and how it would translate to the general U.S. population.

As noted above, prior to selecting a control group, it is imperative that the device indications be appropriately defined. The device indications dictate the process of identifying a proper control group and directing the design of the pivotal clinical trial, length of the study, and primary and secondary endpoint selections. Most nucleus arthroplasty devices are indicated for mild to moderate DDD or instances of acute disc herniation. Use of nucleus arthroplasty devices to address such indications will require a two-year clinical study. In addition, post-market follow-up for a minimum of five years may also be requested. Appropriately describing the indications for the intended patient population may well determine the success of the study and the device itself.

Lastly, establishing the appropriate study endpoints is very important, as they provide the foundation for the demonstration of safety and effectiveness as well as supporting evidence for the device labeling claims. If a manufacturer chooses to exclude relevant endpoints in order to avoid risks or save money, the trial results may be inadequate to support safety or effectiveness, and may greatly weaken the manufacturer's ability to make labeling claims regarding the device performance. Therefore, a complete and thorough study of all potential study parameters is recommended, including radiographic, economic, and clinical assessment measurements.

SUMMARY

Nucleus arthroplasty has the potential to be an excellent treatment alternative for patients in the mild to moderate stages of DDD. Today, this represents a relatively large unmet opportunity for advancements in patient care. However, there are still many unanswered questions that must be addressed before this device technology can be considered a viable treatment alternative. As more clinical data becomes available, manufacturers and the FDA will continue to develop the expertise required to more appropriately design and evaluate such devices. Until that time, individual devices must be examined and studied very carefully on a case-by-case basis.

ABOUT THE AUTHOR

Mr. Stiegman manages and directs the regulatory affairs for a number of VB portfolio companies and other MCRA clients. Mr. Stiegman also prepares marketing submissions for the FDA and assists with the development of global regulatory strategy for VB portfolio companies. Prior to joining MCRA in February 2006, Mr. Stiegman served as the Chief of the Orthopedic Devices Branch for US Food and Drug Administration. As Branch Chief, Mr. Stiegman managed a team of scientists, clinicians, and engineers in the regulation of all orthopedic devices marketed in the United States. In addition, Mr. Stiegman was responsible for overseeing all FDA guidance documents and FDA policy determinations for orthopedic devices marketed in the US. Furthermore, he assisted in and oversaw all integrity, compliance, and monitoring issues regarding the orthopedic industry in collaboration with the Office of Compliance. He also was a member of several leveraging groups such as the Orthopedic Device Forum and Orthopedic Surgical Manufacturer Association, where he represented the FDA. As the head of the Orthopedic Devices Branch, Mr. Stiegman pursued the advancement and consistency in the regulation of all orthopedic devices. This was evident by the pursuit of reclassifying several types of orthopedic devices, developing guidance documents on state-of-the-art orthopedic devices, and educating and assisting the orthopedic community in the regulatory strategies to get devices to market. Prior to becoming Branch Chief, Mr. Stiegman was a reviewer in the Orthopedic Devices Branch where he was the team leader on many state-of-the-art spinal technologies. He was a leader in the field of artificial disc replacements, nucleus replacements, posterior stabilization systems, and many of the current widely used fusion spinal systems. He authored a guidance document for industry on spinal systems indicated for fusion, and he also developed documents that assisted companies in getting other devices to market such as artificial disc replacements, nucleus replacements, and posterior stabilization systems. Mr. Stiegman received his Bachelor in Science at Tulane University in Biomedical Engineering and his Master in Science at Clemson University in Bioengineering with a focus on biomaterials and biomechanics.

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About MCRA

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