Chapter 6 Nucleus Arthroplasty™ Technologies

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INTRODUCTION

Nucleus Arthroplasty™ motion preservation technology represents a novel treatment approach in which the degenerated nucleus pulposus is replaced via surgical intervention. The goals of Nucleus Arthroplasty surgery are to preserve the motion and geometry of the index intervertebral disc while preventing adjacent segment degeneration. Such technologies will prove to be of great appeal when considering the unique clinical challenges associated with the management of degenerative disc disease (DDD) in young active patients. If the condition is inadequately treated with conservative care, progression is predictable. Definitive treatment with fusion surgery is similarly problematic.

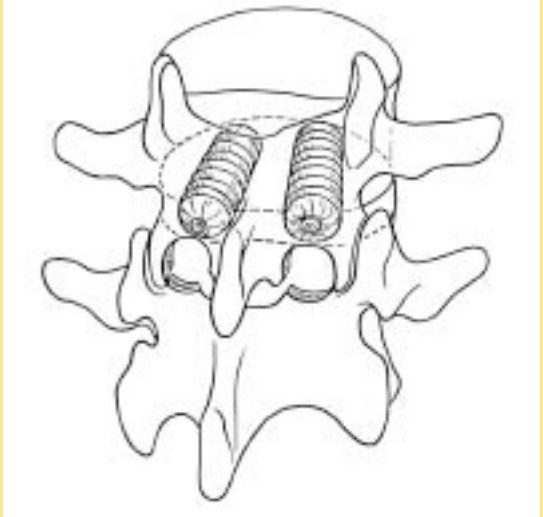
One of the most evident signs of increasing interest in Nucleus Arthroplasty technology is the involvement of several major spine companies in the development of Nucleus Arthroplasty devices. The marketing resources of these industry leaders will serve to increase general awareness of disc Nucleus Arthroplasty technology as a successful treatment option and increase the number of surgeons trained in these technologies.

DISC NUCLEUS ARTHROPLASTY DEVICES DATE BACK TO THE 1980S WHEN CHARLES D. RAY, MD, FACS CONCEPTUALIZED A TWO-PILLOW HYDROGEL NUCLEUS ARTHROPLASTY DEVICE.

THE HISTORY OF NUCLEUS ARTHROPLASTY DEVICES

Disc Nucleus Arthroplasty devices date back to the 1980s when Charles D. Ray, MD, FACS conceptualized a two-pillow hydrogel Nucleus Arthroplasty device. The original Raymedica PDN® device was completed in 1995, and the first human implant occurred in 1996. Dr. Ray's original design has since been replaced by single-pillow designs, the Raymedica PDN-SOLO® and HydraFlex™ devices.

The Stryker Howmedica Osteonics Aquarelle is another example of an early disc Nucleus Arthroplasty device. Qi-Bin "Chip" Bao and Hansen Yuan, MD, worked on this device, which was made of polyvinyl alcohol (PVA), another hydrogel-based technology. The technology was tested in both animal and biomechanical studies. However, it is believed that this product is not currently available commercially due to adverse events encountered in preliminary studies.



Early Drawing of Nucleus Arthroplasty Device by Charles D. Ray, MD, FACS

CURRENT NUCLEUS ARTHROPLASTY DEVICES

More than 20 different Nucleus Arthroplasty devices are currently in the concept or development stage. These devices use hydrogel, polymer/synthetic, or mechanical technologies. Devices using these technologies are as follows:

Hydrogels

- PDN-SOLO® and HydraFlex™ devices – Raymedica, LLC
- NeuDisc™ – Replication Medical, Inc.
- Gelifex family of hydrogels – Synthes, Inc.

Polymers/Synthetics

- DASCOR™ – Disc Dynamics, Inc.
- NuCore™ Injectable Nucleus Device – Spine Wave, Inc.
- SINUX ANR – Sinitec, AG/DePuy Spine, Inc.
- BioDisc™ – CryoLife, Inc.

Mechanical

- EBI Regain™ – Biomet, Inc.
- NUBAC™ – Pioneer Surgical Technology

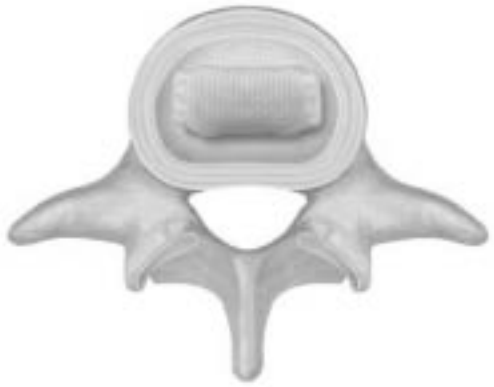
Each of these technologies and/or devices will be discussed in some detail in the following sections.

HYDROGEL TECHNOLOGIES

The majority of preformed Nucleus Arthroplasty devices feature soft hydrogel cores that provide flexibility and absorb/release water gradually (disc "breathing"). The implants are designed to exhibit the weight-bearing characteristics seen in the natural nucleus and maintain disc space height and mobility in the intervertebral segment.

PDN-SOLO AND HYDRAFLEX – RAYMEDICA, LLC

Raymedica pioneered the field of Nucleus Arthroplasty motion preservation systems and is the first company to widely promote physiological restoration of the form and function of the disc nucleus. The company was founded in 1990 by Charles D. Ray, MD, FACS.



The current design of the Raymedica family of Nucleus Arthroplasty devices features a pellet-shaped hydrogel core enclosed within a constraining jacket composed of woven, high molecular weight polyethylene. The constraining jacket is flexible, yet inelastic and porous allowing fluid to pass through to the hydrogel core while maintaining the shape memory of the device. After implantation, the hydrogel core immediately begins to absorb fluid and expand within the disc space. This design emulates the natural human disc nucleus, which responds to physiological loading by expanding or compressing to provide the necessary support for the spinal segment. Raymedica's technology also incorporates the use of platinum-iridium wire markers embedded in the hydrogel core. The wires allow radiographic visualization of the device during and after the procedure.

The company has utilized this proprietary preformed hydrogel technology to develop a range of devices with varying size, shape, and axial load strength/stiffness characteristics to meet the needs of individual patient anatomies.

Raymedica's technology is currently utilized in two product platforms:

- **PDN-SOLO® –** The PDN-SOLO device is a single-unit implant designed to replace the diseased nucleus and restore disc height. The PDN-SOLO device can be implanted via a posterior PDN approach (PPA) or an AnteroLateral transPsoatic Approach (ALPA). PPA allows direct decompression with access to the disc space via laminotomy. ALPA provides direct lateral access to the disc space with no disruption of the posterior elements. The PDN-SOLO device exhibits outstanding flexibility allowing delivery through either anatomic approach. The device also provides conformability to adapt to the human intervertebral disc space.
- **HydraFlex™ Nucleus Arthroplasty System™ –** This fourth generation technology is Raymedica's latest system designed to replace the diseased nucleus and maintain disc height. The HydraFlex is implanted via an Anterior lateral RetroPeritoneal Approach (ARPA). This approach permits control of the annular incision and is less destabilizing to the index segment compared to the traditional posterior approach. The HydraFlex device is designed with the same proprietary preformed hydrogel technology that has been implanted for more than 10 years. However, this device has distinctly different design features compared to the PDN-SOLO device. The HydraFlex NAS features a more anatomic contoured shape for a greater fit and fill, a softer core with a larger footprint to reduce the risk of subsidence, and faster hydration for quicker stabilization. The HydraFlex NAS also incorporates specially designed instrumentation to facilitate repeatable/reproducible intradiscal sizing and precise implant placement to improve clinical performance.

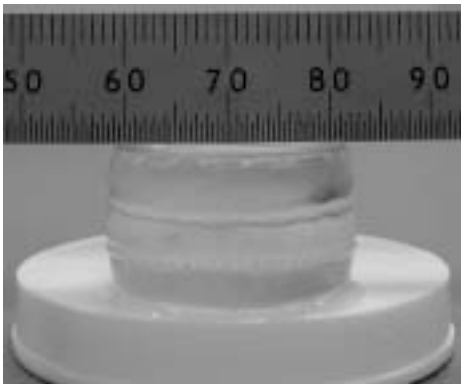
Neither the PDN-SOLO device nor the HydraFlex NAS are commercially available in the U.S. All non-fusion spinal implants, including Raymedica's devices, are considered Class III medical devices and require Pre-Market Approval (PMA) from the Food and Drug Administration (FDA) prior to market release in the U.S. Raymedica's goal is to achieve PMA approval for the HydraFlex NAS, the fourth generation PDN implant, by 2011. It is Raymedica's belief that the HydraFlex NAS will be one of the first Nucleus Arthroplasty devices to achieve PMA approval from the FDA if this goal is met. The company received conditional FDA approval in June 2006 to begin enrolling patients in a U.S. feasibility study to evaluate the potential benefits of the HydraFlex NAS for the treatment of DDD.

Raymedica, LLC is a privately held company headquartered in Minneapolis, Minnesota. The company currently has CE Mark approval for the PDN-SOLO and HydraFlex devices and is marketing the PDN-SOLO device in 11 countries. Raymedica is the pioneer and leader in Nucleus Arthroplasty motion preservation technology as a result of the extensive clinical experience gained from over 4,600 implants worldwide since 1996.

NEUDISC – REPLICATION MEDICAL, INC.

Replication Medical, Inc. (RMI) was formed in 2000 to develop and commercialize the company's proprietary hydrogel implant technology. The company's sole initial focus is the development of the NeuDisc spinal nucleus implant. The NeuDisc device is designed to replace the native nucleus pulposus and restore function to the disc, potentially slowing or reversing the degenerative process.

THE NEUDISC DEVICE IS DESIGNED TO REPLACE THE NATIVE NUCLEUS PULPOSUS AND RESTORE FUNCTION TO THE DISC.



The company is developing a spinal nucleus implant (NeuDisc™ Radially Anisotropic Spinal Nucleus Implant) device made of modified polyacrylonitrile polymer, hydrolyzed to yield a hydrophilic biocompatible polymer gel. The unique feature of this material is that it can take up 90% of its weight in aqueous solutions, which is similar to the water content of nucleus pulposus. When the device is subjected to large loads, it dehydrates and its stiffness increases. Thus, it responds to loads in a manner similar to that of nucleus pulposus. The NeuDisc is inserted in a dehydrated state, facilitating minimally invasive implantation, and then expands anisotropically after insertion due to water absorption. The implant is manufactured from a synthetic polymer, a multiblock acrylic copolymer produced by partial hydrolysis of polyacrylonitrile.

The NeuDisc implant, containing H-PAN hydrogel, is delivered in a semi-hydrated state, intended to allow implantation through a smaller nucleotomy incision and consequently decreasing the chances of device migration. Due to the way the H-PAN is layered in the implant, it rehydrates anisotropically within the disc space meaning that it expands preferentially in the axial direction. A jacket is not required due to the internal structure of the devices featuring a series of polymer layers tied together with an internal substructure. The tethering prevents the material from deforming and creeping. This is an important feature, because the goal of an implant is to fill the space of nucleus pulposus completely without changing its diameter after implantation.

A significant amount of mechanical and pre-clinical testing has been performed on the NeuDisc including compression to failure, fatigue, cadaver, motion, and biocompatibility testing. The majority of tests have been performed in the U.S., though the NeuDisc is not commercially available in the U.S. and is currently being implanted in fewer than 10 centers in the European market.

GELIFEX FAMILY OF HYDROGELS – SYNTHES, INC.

Synthes, Inc. is developing two polymer-based hydrogels as minimally invasive injectable nucleus replacement technologies after acquiring Gelifex, Inc. in April 2004. The Gelifex SP and Gelifex IP hydrogels are liquid at room temperature and solidify inside the core of the disc at body temperature. Anthony Lowman, PhD, who developed the technology at Drexel University, describes the material as having the properties of a porous rubber ball. When the material is introduced to water, the pores fill to restore the natural height of the disc segment. Synthes is also working on a second-generation product. This hydrogel is also liquid at room temperature and designed to solidify inside the disc space at body temperature. The product will be delivered via a very small needle through an incision that will not damage the annulus. Currently, the technology is not commercially available and is undergoing pre-clinical testing. Pre-clinical biomechanical testing on cadavers was completed in 2003 and preliminary results show that the hydrogel holds up well matching the properties of the intact spine.

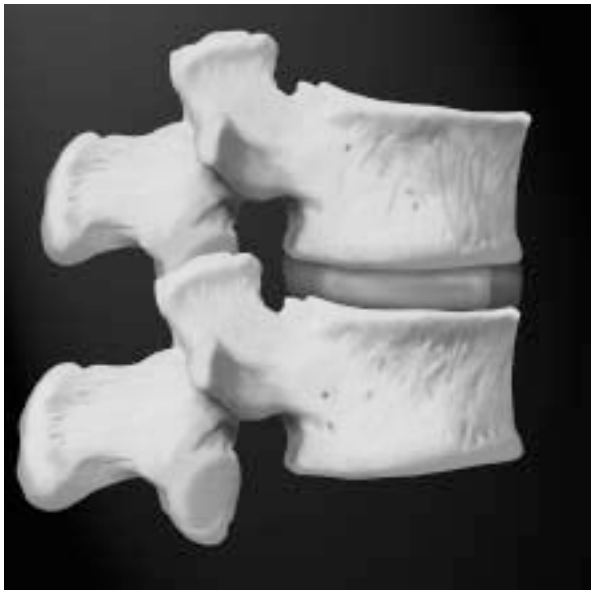
POLYMER/SYNTHETIC TECHNOLOGIES

The concept behind injectable devices using polymer/synthetic technologies is to deliver the nucleus replacement implant in a semi-liquid state that then solidifies within the disc space. Substrates used to date are flexible hydrogels including silk-protein polymers, serum albumin polymers, and polyurethanes. It is hypothesized that the ability to deliver the device through a smaller annulotomy and achieve a unique or "perfect fit" within the disc space will reduce the risk for device migration. The goals for the injectable devices are the same as the preformed devices, namely preservation of both disc space height and segmental motion.

DASCOR DISC ARTHROPLASTY SYSTEM – DISC DYNAMICS, INC.

The original concept for the DASCOR system was derived from the Advanced Bio-Surfaces knee surgery research program encompassing extensive *in vivo* and *in vitro* studies designed to demonstrate the biocompatibility and mechanical properties of an *in situ* curable polyurethane polymer technology. Disc Dynamics, Inc., a private company headquartered in Eden Prairie, MN, was founded in May 2000 as a spin-off of Advanced Bio-Surfaces with the goal of developing and commercializing curable polymer technology for applications in the spine.

The delivery method for the DASCOR system is based on technology used in interventional cardiology. The DASCOR device is delivered using a catheter and balloon approach under controlled pressure via an injection pump and cures *in situ*. The system is designed to minimize the incidence of migration, because the polyurethane polymer is delivered under pressure and completely fills the void left by the removal of the nuclear material. The polyurethane used in the implant has demonstrated mechanical strength and durability, while maintaining a low modulus. It is the belief of Disc Dynamics that the polyurethane polymer is an ideal biomaterial for disc replacement due to its well-established biocompatibility profile, superior mechanical strength, and elastic properties. The material makes it possible to use a delivery balloon that is robust but compliant with the ability to expand during polymer injection, fill, and conform to the individual patient's nucleus cavity while distracting the disc space and maintaining disc height. Thus, the technology creates an individualized solution for each patient.

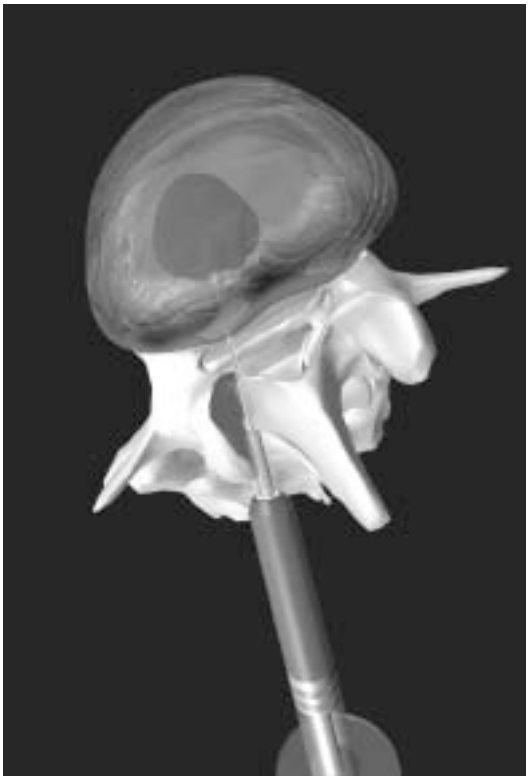


THE DASCOR DEVICE IS DELIVERED USING A CATHETER AND BALLOON APPROACH UNDER CONTROLLED PRESSURE VIA AN INJECTION PUMP AND CURES *IN SITU*.

The device is implanted through a very small (5 mm) hole in the annulus. The size of the required annulotomy incision is significantly smaller than that demanded by other devices and should reduce the risk of implant extrusion. Although, the risk for extrusion is lower, the device, as with all nucleus replacement devices, clearly requires the presence of a relatively healthy annulus, as determined by pre-operative discography.

DASCOR has been in clinical use outside the U.S. since 2003 but is not commercially available in the U.S. Disc Dynamics received CE Mark approval for the commercial sale of the technology in the European Union in July 2005. In August 2006, the company announced it received FDA approval to start a pilot clinical study of the DASCOR device.

NUCORE IS AN INJECTABLE PROTEIN-BASED NUCLEUS REPLACEMENT TECHNOLOGY FORMULATED ON PROPRIETARY TISSUE ADHESIVE TECHNOLOGY.



THE NUCORE MATERIAL IS COMPRISED OF A BINARY FORMULA OF A CHEMICAL CROSS-LINKER AND A PROTEIN CO-POLYMER SOLUTION THAT CURES RAPIDLY *IN SITU* FORMING A DURABLE, ADHESIVE HYDROGEL WHEN INJECTED INTO THE DISC NUCLEUS SPACE.

NUCORE INJECTABLE NUCLEUS DEVICE – SPINE WAVE, INC.

NuCore is an injectable protein-based nucleus replacement technology formulated on proprietary tissue adhesive technology.

The NuCore material is comprised of a binary formula of a chemical cross-linker and a protein co-polymer solution that cures rapidly *in situ* forming a durable, adhesive hydrogel when injected into the disc nucleus space. When cured, the injected material has been shown to be very resistant to extrusion events seen in other nuclear devices in extensive pre-clinical bench and animal testing. This is primarily the result of two factors: First, the bolus of cured NuCore material is much larger than the surgical entry site, thus forming a mechanical barrier. Second, the hydrogel's adhesive properties contribute to its ability to resist extrusion.

The surgical technique used with NuCore involves mixing the binary liquid of the silk elastin polymer with the chemical cross-linking agent just prior to injecting them in a minimally invasive fashion through a syringe. The injected material fills the void left when nuclear material is removed during discectomy. The liquid polymer cures rapidly *in situ* forming a tough, adhesive material.

Spine Wave, Inc. was created in April 2001 to develop the NuCore technology. Animal studies and pre-clinical testing has been conducted, though NuCore is not commercially available in the U.S. In February 2006, Spine Wave announced it was beginning patient enrollment in a feasibility IDE clinical trial studying NuCore as an adjunct following a standard microdiscectomy procedure to fill the void created after herniated nuclear material is surgically removed. In June 2006, the company announced it was beginning patient enrollment in a second arm of the feasibility IDE clinical trial studying NuCore for the treatment of DDD.

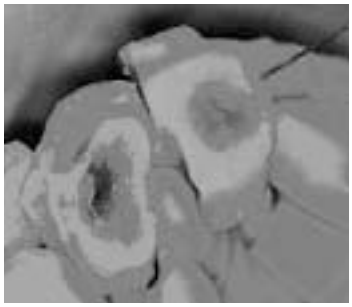
SINUX ANR – SINITEC, AG/DEPUY SPINE, INC.

The SINUX ANR is a liquid polymethylsiloxane (PMSO) polymer that is injected into the disc with enough pressure to completely fill the void left after removal of nuclear material. The polymer cures *in situ* into a resilient elastic mass in approximately 15 minutes without a constraining jacket. The procedure is minimally invasive and can be performed with a standard discectomy approach. Following implantation of the device, the annulus is sutured. The SINUX ANR was developed as a nucleus replacement technology to treat degenerated discs in the lumbar spine and is commercially available in Europe under the CE mark obtained in January 2004.

Jan Zoellner, MD, of the Orthopädische Klinik in Johannes Gutenberg, Germany invented the SINUX ANR technology after witnessing the high rate of post-discectomy syndrome and failed back syndrome resulting from the use of rigid systems. Sinitec, AG, a German-based company that was founded in 1999, signed an exclusive distribution agreement with Depuy Spine in 2003. The SINUX ANR device was shown first shown by Depuy Spine at the Eurospine Conference in Prague in August 2003.

BIODISC INTERVERTEBRAL DISC REPAIR SYSTEM – CRYOLIFE, INC.

The BioDisc system is designed for implantation after the disc nucleus is removed. Upon injection into the nuclear cavity, the substance solidifies to form a spacer that provides disc space distraction, while acting as a glue to bind the vertebral bodies. The material composition of the BioDisc system is a CryoLife proprietary product resulting from the *in vivo* mixture of a protein solution (serum albumin) and a cross-linking component (gluteraldehyde). The two solutions are kept in separate chambers



prior to exposure inside the wall of the annulus and mix as liquids *in vivo* forming a polymerized matrix. The hydrogel solidifies as a pliable support solid within the disc space. The BioDisc material is similar to epoxy glue and is composed of the same base material used in CryoLife's BioGlue surgical adhesive. However, the formulation for the BioDisc differs from that of the BioGlue to address use in spinal applications.

The BioDisc material is injected in liquid form from a two-chamber cartridge, which is stored at room temperature. It is believed that the procedure can be performed percutaneously, where the product is injected via a 22-gauge syringe under fluoroscopic control. The substances mix and become 90% solid within 30 seconds of implantation and solidify completely within two minutes. No heat is generated from the insertion of the material.

Currently, the technology is not commercially available. The company has completed Phase I and II pre-clinical animal and bench testing. Enrollment of patients in the BioDisc spinal disc repair system study was completed in July 2006. The 10-patient study being conducted in the United Kingdom is designed to gather basic safety and performance data. The study targets patients with disc herniations in the lumbar spine at the L4/L5 and L5/S1 vertebral levels.

CryoLife, Inc., founded in 1984, is a life sciences company involved in the development and commercialization of cryo-preserved and tissue-engineered implantable heart valves, vascular and orthopedic grafts, and surgical adhesives.

SINUX ANR IS A LIQUID POLYMETHYLSILOXANE (PMSO) POLYMER THAT IS INJECTED INTO THE DISC WITH ENOUGH PRESSURE TO COMPLETELY FILL THE VOID LEFT AFTER REMOVAL OF NUCLEAR MATERIAL.

MECHANICAL TECHNOLOGIES

Preformed implants composed of hard materials including metal alloys, polyetheretherketone (PEEK), pyrolytic carbon, or zirconia ceramic have been developed. These implants are in contact with both endplates and transmit forces across the disc space.

REGAIN DISC – BIOMET, INC.

The Regain disc is a rigid one-piece device composed of pyrolytic carbon that is held in the disc space by the natural bony anatomy of the endplate. The implant geometry is designed to maintain disc height and to provide for normal motion of the lumbar spine. The Regain device is highly polished to prevent damage to the cartilage on the vertebral endplates, and the material has a modulus of elasticity nearly identical to bone. Pyrolytic carbon has a long history of use in the human body including use in mechanical heart valves and has not shown biocompatibility issues.

The Regain technology was developed by Biomet's EBI division in conjunction with Steve Cook, MD, of Tulane University.

The accompanying figure shows the implant design used in lumbar nucleus replacement. EBI and Dr. Cook have also developed a cervical nucleus replacement device.

The Regain device has undergone significant testing and has had comprehensive bench and cadaver tests. The lumbar device has been studied in eight baboons and the cervical device has been studied in 20 dogs. Updates from the 2005 and 2006 Spine Arthroplasty Society meetings reported no operative complications, evidence of device migration, neurological compromise, or subsidence after one-year follow-up, although remodeling and sclerosis were noted. The dog study represents a worst-case scenario for the technology because the shape of the dogs' endplates is opposite that in humans. Currently, the Regain device is not commercially available in the U.S. and is being implanted in limited human clinical trials in Europe. It is anticipated that Biomet will start a U.S. clinical trial for the Regain device in September 2006.

Biomet, established in Warsaw, Indiana in 1977, is one of the world's largest orthopedic companies with sales of more than $2 billion annually in more than 100 countries and more than 5,000 employees.

NUBAC – PIONEER SURGICAL TECHNOLOGY

The NUBAC disc arthroplasty device is made from PEEK-OPTIMA; a material that is currently being commercialized in spinal fusion implants. NUBAC is the only intradiscal arthroplasty device for patients with degenerative disc disease utilizing articulating PEEK-on-PEEK material designed to achieve load sharing and uniform stress distribution under various physiological loading conditions. By providing even stress distribution with its inner-articulating feature, the NUBAC implant is designed to minimize potential subsidence and extrusion risks as well as maintain disc height. The NUBAC procedure is intended to conserve most of the annular tissue and to be less invasive than total disc replacement and fusion allowing further treatment options if revision is required. Currently, the technology is CE marked and being implanted in a limited, controlled fashion in both Europe and Asia Pacific. NUBAC received conditional approval from the FDA to proceed with a feasibility study in July 2006, and the first patient was enrolled in August 2006.

Pioneer Surgical Technology, headquartered in Marquette, Michigan, is a privately held company specializing in the design and manufacture of spinal and orthopedic implants. The company was founded in 1992 and currently employs over 200 employees worldwide.