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Small Bone Innovations, Inc.
The Artelon® family of bioabsorbable spacers, marketed by Small Bone Innovations, Inc., was developed for patients with osteoarthritis (OA) in the base of the thumb. The Artelon® CMC Spacer is a T-shaped, woven construction made of fibrous material consisting of a degradable polyurethane-urea biomaterial shown to act as a supporting scaffold to stabilize the joint and aid tissue re-growth.

The Artelon CMC implant was introduced in the U.S. in 2005 to treat early- to mid-stage OA in the thumb. This is one of the most common forms of OA in the upper extremity. Since then, more than 900 surgeons have been trained worldwide in the use of Artelon. The Artelon implant is designed to achieve both resurfacing and stabilization of the osteoarthritic trapezio-metacarpal joint (also known as the carpo-metacarpal joint). The purpose of the vertical portion is to separate the surfaces of the arthritic joint and to act as a spacer between the trapezium and the first metacarpal. The horizontal portion acts to stabilize the joint. Another spacer, the Artelon® STT, is available to treat the adjacent scapho-trapezio-trapezoidal joint.

By using the Artelon CMC Spacer the trapezial bone will be preserved, thus keeping the original anatomy of the hand virtually intact. This avoids shortening of the thumb and provides significantly better pinch strength compared to other therapies. Surgery is normally performed under regional anesthesia.

SBI has an exclusive worldwide licensing agreement (excepting the Nordic countries) with Artimplant AB of Sweden, the developer of Artelon technology. It covers the four versions of spacer technology now available to surgeons in the U.S., as well as all future resurfacing and interposition applications in the fingers, hand and wrist domain.

Small Bone Innovations, Inc.
1380 South Pennsylvania Avenue
Morrisville, PA 19067
Main: 215-428-1791
Customer Service: 800-778-8837
www.totalsmallbone.com
Enquiry No 1
Dear Doctor,

In 2007, you and your colleagues performed 16 million orthopaedic procedures. In the overwhelming number of cases, the result for the patient was dramatic.

I used to look forward to discussions with surgeon friends. We’d spend quality time enumerating clinical challenges and speculating on the technology solutions. I always left these talks in a state of elation. While there were still concerns and challenges, the system had the resources and fine minds to address them. Now it seems that the main subject on everyone’s mind is the Department of Justice.

Some write it off as political parrying before the national election. Others pontificate that it is a long overdue overhaul of an archaic and corrupt system. Most everyone in the know agrees that it is far from over, and most are in agreement that regardless of what restrictions are placed on the system, we cannot forego the surgeons input into product design and technology development. For those of us involved in the art, science and industry of orthopaedic care, this states the obvious. I would, however, feel more comfortable if those proposing legislation felt a little more strongly about it. Apropos to this, we feature inside this issue a summary of DOJ activity in orthopaedics and spine along with the motivations of the lawmakers pursuing change. This comes in the form of testimony by Greg Demske of the Office of Inspector General. Some would feel better if he were an orthopaedic surgeon, or at least knew one to talk to.

This whole debacle threatens to drive a wedge between industry, surgeons and the patient. The further the wedge goes, the deeper the rift between patient needs and the system’s ability to address them. No one wins.

On the pages herein, critics of the system see expensive and wasteful results of medical payola. The informed realist cannot help but feel excited and fulfilled by the plethora of technologies developed in direct response to the sometimes urgent needs of the millions of patients that you treat each year. We sincerely hope that the latter perspective is what will guide those who decide the fate of you and your patients in the form of healthcare reform legislation.

John A. Engelhardt
Editor in Chief
PROVEN FOR YOUR COMPLEX SPINAL PATHOLOGIES

K2M’s one focus, the spine. The RANGE™ Spinal System, a fusion of DENALI™ and MESA™, offers a complete array of reduction techniques, unique and low-profile screws, rod connectors, and hooks. Coupled with exciting innovations in instrumentation, this comprehensive system is poised to address the entire range of complex spinal pathologies.

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Before addressing the topic of this article, I am pleased to provide an update to my previous article entitled “The Rules of the Road Are Changing For Patents” (November/December 2007). As I reported in an earlier addendum to that topic (January/February 2008), the U.S. District Court, Eastern Division of Virginia on October 31, 2007 issued a Preliminary Injunction enjoining the U.S. Patent and Trademark Office (USPTO) from implementing the changes in the Claims and Continuations Final Rule. Some of my concerns to the proposed changes to the rules of practice in the Claims and Continuations Final Rules were briefly discussed in my previous article to which your attention is invited. The rule changes were originally scheduled to go into effect on November 1, 2007. As mentioned above, that implementation date was temporarily enjoined the day before the scheduled implementation of the Final Rules. Following extensive arguments, the District court found that the USPTO was not empowered by law to make substantive rule changes and further determined that the Final Rules proposed by the Patent Office are neither procedural rules nor rules relating to application processing that have substantive collateral consequences, but rather are substantive rules that change existing law and alter the rights of patent applicants under the Patent Act. The District court determined that the Final Rules constituted a drastic departure from the terms of the Patent Act and in doing so, effect changes in the existing rights and obligations of patent applicants. As discussed in my previous article, the proposed Final Rules would have effectively shifted much of the prior art search and analysis burden to the applicant and thus increased the patent applicant’s expenses for legal fees. This court decision is very good news for the patent applicant. While it is very likely that the USPTO will appeal the decision, it is not considered likely that the court’s decision will be reversed. We will continue to follow this matter and report its progress.

Now turning to the topic at hand, patent prosecution, let us first consider who is involved and what role they play. Patent prosecution is the process of exchange between the patent applicant with his patent attorney and the U.S. patent examiner. The process would ideally begin immediately after the patent application is filed with the USPTO. Rather than “immediately,” the time line between the patent application filing date and the date that the patent examiner first begins his reading and examination of the application would better be described as “directly.” Patent applicants should understand from the beginning that patent prosecution is not a quick process.

Within a few weeks, the newly filed patent application will be assigned to the Office of Initial Patent Examination. This office is tasked with examining the newly filed patent application only for the purposes of determining if the application is formally complete; that is, it meets all of the requirements specified for a complete and correctly filed application. Any necessary supplemental papers that must be filed, such as an inventor’s declaration, will be requested by the Office of Initial Patent Examination, and the patent applicant and his attorney will respond accordingly. This initial exchange between the patent applicant and the Patent Office is generally handled very quickly and efficiently.

At this point, efficiency takes a back seat to the frustration of a growing queue of backlogged patent applications awaiting examination in the Patent Office. Upon completion of the initial examination for compliance with formalities, the patent application will be assigned to one of eight distinct Technology Centers. They are: Technology Center 1600, Biotechnology & Organic Chemistry; Technology Center 1700, Chemical and Materials Engineering; Technology Center 2100, Computer Architecture, Software & Information Security; Technology Center 2600, Communications; Technology Center 2800, Semiconductors, Electrical and Optical Systems and Components; Technology Center 2900, Designs; Technology Center 3600 Transportation, Construction, Electronic Commerce, Agriculture, National Security, and License & Review; and Technology Center 3700, Mechanical Engineering, Manufacturing and Products & Design.

It is in Technology Center 3700 where inventions in the surgical arts will be examined. Occasionally an invention will spill over into more than one area of technology, for instance, in a device such as a trocar or cannula (Tech Center 3700) that also includes a laser or optical device (Tech Center 2800) or mechanical surgical implants (Tech Center 3700) that might include chemical coatings (Tech Center 2100) or inclusions of genetically engineered tissues (Tech Center 1600). Such hybrid inventions in the surgical arts are assigned to the surgical art unit within the mechanical technology center.

Common to each of the Technology Centers is a prolonged delay in bringing a patent application to the initial examination on the merits by a patent examiner. It is not uncommon now for a patent application to wait as long as two years before it is first examined and an initial Office Action on the merits sent to the patent applicant. The disappointment of such a prolonged waiting period can be frustrating for the patent applicant who, from the time of his conception of the invention, has worked expeditiously to obtain patent protection and develop the invention commercially. This time of patent pendency need not be unproductive.
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Questions? Contact Terry Paolino: 781.433.1239 • paolino@jbjs.org

Enquiry No 5
Frequently, during this early waiting period, much of the work is done to develop manufacturing, development and marketing alliances through contracts, licenses, or assignment of the patent pending invention.

The patent prosecution phase begins with the patent examiner’s initial examination of the patent application on the merits. The examiner will initially search the prior art in an attempt to identify any publicly known (published) art that discloses the elements of the patent applicant’s invention, as defined by the claims. While the examiner may discover a singular prior art document that discloses the claimed invention in its entirety, it is more often the case that the examiner will find two or more prior art disclosures that when combined will render the applicant’s invention obvious to one of ordinary skill in the art. Through this process the examiner will in this initial examination endeavor to reject the claimed invention as not novel, or as obvious over the prior art of record. The examiner will communicate by letter his Official Action to the patent applicant through the patent attorney and will set a date three months from the date of mailing by which a response to the rejection must be filed with the Patent Office. This due date is extendable to a maximum period of six months.

Upon receipt of the examiner’s Official Action, the patent attorney will consult with the patent applicant to determine if the examiner is accurate in his assessment of the claimed invention in light of the prior art found. Every detail of the claim can be important in making a patentable distinction between the prior art and the claimed invention. Careful consideration is the governing rule of this exercise in preparing a response. At times, the response to the examiner can be entirely in the form of argument which overcomes the initial conclusions of the examiner in his rejection of the claims. At other times, the claims may require an amendment to add or modify an element of the claims so as to distinguish the applicant’s invention from that disclosed in the prior art. Upon submission of the response to the Patent Office, the applicant and his attorney again will patiently await the progress of this communication through the ever-lengthening queue of the examiner’s docket.

Ideally, the examiner will once again consider the patent application with the recently received applicant’s response/amendment within three to four months from the time of response submission. This delay can be shorter or longer, but more and more often it is becoming longer. The backlog of communications awaiting the examiner’s consideration continues to grow each year. However, this prolonged time of waiting can be put to good use. Often, in license or assignment negotiations, prospective licensees/assignees will want to discuss the status of the pending application. If the examiner’s initial rejections of the claims were weak or easily overcome by the applicant’s response, the prospective licensee/assignee will be encouraged to strike a deal with the patent applicant and his attorney again will patiently await the progress of this communication through the ever-lengthening queue of the examiner’s docket.

Should the examiner disagree with the patent applicant’s After Final arguments and amendments and persist in his rejection of the claims, he will mail an Advisory Action to the applicant that briefly states his position of maintaining the rejection of the claims. While it is not required, some patent attorneys, who sincerely appreciate their role in bringing new technology to the public and for the public good, will at this point still entertain an additional communication from the applicant that seeks to place the patent in condition for allowance. Such additional consideration is not the rule and cannot normally be expected in the course of patent prosecution. At this point, the patent applicant can exercise different options.

If in fact the patent applicant and his attorney believe that the examiner was right in his assessment of the claims of the application and indeed they are not allowable over the prior art of record, the patent application can be allowed to go abandoned. Alternatively, if the patent examiner is believed to be correct in his rejections, the patent application can be re-filed as a Continuation-in-Part (CIP) application that would then contain additional disclosure materials, additional elements, improvements or data that was lacking in the initial/parent application. Such additions to the CIP application may be necessary to overcome the prior art upon which the claims of the parent application were rejected. A CIP application is an entirely new application that has its basis in the disclosure of the original and claims priority for that information to the original filing date.

If the patent applicant persists in his belief that the examiner was incorrect in his rejections of the claims of the original application, he can appeal the examiner’s decision to the Board of Patent Appeals and Interferences. It is not uncommon for the board to reverse a decision of
The pathway to patent protection can be long and arduous, and certainly can become expensive to follow in some cases. The prolonged delays now experienced by patent applicants in their quest to obtain patent protection continue to increase each year, adding to the frustration of a patent prosecution process that can easily require two, three or more years to complete. The inventor/entrepreneur embarking on that journey must know at the outset that obtaining patent protection is not quick, simple or inexpensive—and with that also understand that no one can guarantee the final outcome of the patent prosecution process.

The intention of this article is only to provide the reader with a general understanding of the dialogue between the patent applicant and the patent examiner that constitutes the framework of patent application prosecution. While a telephonic or personal interview between the patent applicant and his attorney with the patent examiner may occur, the process is basically an exchange of carefully crafted correspondence over a one to three year period, which may or may not result in an issued patent protecting the exclusive rights of the patentee to his claimed invention. As such, this article is not intended as legal advice but is provided only to assist the inventor/entrepreneur in his understanding of the patent prosecution process.

Perry Van Over is the Founding Member of Perry E. Van Over & Associates, PLLC, an intellectual property law firm specializing in patent procurement, licensing and litigation in the technical fields of surgical instruments, medical devices, molecular biology, pharmaceuticals, biochemistry and polymer chemistry. He can be reached at 703-543-6456 or perryvanover@cox.net.

Enquiry No 23

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Enquiry No 6
The Functions of Effective Marketing

Having worked with orthopaedic practices for nearly twenty years, it has become readily apparent that practices staff and outsource their marketing efforts in various ways. Regardless of size or sophistication, nearly every practice engages in numerous marketing functions. The following outlines each of the primary functions and its role in serving your practice.

Business Strategy

Business strategy is one of the most fundamental elements of good marketing. Without a clear vision of where the practice is going, few practices are truly in a position to maximize the monetary and competitive advantages of effective marketing.

In recent years we have witnessed significantly more business sophistication on behalf of practices. Primarily at larger practices, administrators/CEOs are far savvier and physicians are realizing the importance of managing, running and leading an organization with business fundamentals. We are seeing more planning and forecasting than ever before and this leads inevitably to more efficient and results-oriented marketing.

Marketing Strategy

Marketing strategy is primarily charged with aligning the practice’s vision and tactical business objectives while balancing the needs of the market and available resources such as time, talent, money and commitment. Additionally, an effective marketing strategy requires a methodology that targets a return on investment or return on objective scenarios.

Marketing Coordination

Marketing coordination is primarily an internal function that acts as a liaison between an agency or marketing firm and the practice. This position is usually added when a practice reaches a level of activity that exceeds the administrator’s capacity.

The level of necessary marketing efforts and therefore an effective budget for marketing efforts has little to do with the size of your practice. Activity and budget should be influenced more by the competitiveness of the market and how aggressive your objectives are. If you are in a market with few competitors and minimal objectives, your activity and budget should be far more modest than others. If, however, you do have a significant amount of activity, having some level of marketing coordination may be required.

Project Management

Project management coordinates efforts between all functions such as creative direction, interactive design, copywriting and production along with coordinating vendors and suppliers with the internal marketing coordination. In short, project management is the glue that holds all projects together and delivers a final project.

Outreach Liaison

External relationships make up important and valuable referral sources to orthopaedic practices. An outreach function can be beneficial with specific efforts especially for large practices (30+ physicians) in large markets. In the last few years we have seen practices both hire and contract this function for primary care and Workers’ Compensation segments with variable success. The use of the “right” athletic trainers can be very effective, but like nearly all liaison efforts, the emphasis is on the “right” personnel.

Copy Writing

Marketing is about communicating the right messages. When it comes to orthopaedic practices, numerous messages need to be communicated to several different audiences. Regardless of the organization, whether healthcare or any other, copywriting is one of the most challenging functions. First, and most importantly, copywriting is responsible for communicating a message effectively to those for whom it is intended. Secondly, it has to align with the personality and style of the practice.

Creative Direction

When it comes to effectively communicating a message, creative direction leans heavily on research and guiding principles to drive both verbal and visual messaging. High level creative direction requires a solid understanding of internal and external branding, market mediums and the special needs of the market and its segments.

Most physician groups err in believing that what they have to say is the message. Great copywriting and creative direction will leverage research and communication fundamentals, and develop messaging that the market wants to hear.

continued on page 13
Art Direction and Graphic Design

Art direction and design are specialized functions that utilize visual communications to reinforce key messaging. Good design reinforces the message through various means such as photography, illustration, typography, color schematics and many other potential visual effects. Just as a copy writer utilizes his/her skill set to effectively communicate the strategic message, art directors and designers leverage their skill sets to do the same—just visually.

In all our research, the one thing that stands out is how similar competing orthopaedic practices are viewed by their market. Rarely is there a practice that has truly differentiated itself in the eyes of primary care or prospective patients. This is why good design is so important.

When you consider all the options to truly differentiate your practice to your market and the corresponding efforts, good design is probably the least expensive way to do it. Candidly, I am amazed at how well-dressed orthopaedists are in clinic, whether in white coat or not. Yet, they will have a web site that looks as if it was developed by a local high school kid or have materials that have been photocopied so many times that they are illegible. For some reason, how they present themselves personally often doesn’t line up with how they present their practice.

Interactive Design

Since the onset of the internet in the mid '90s, interactive design has become mainstream in the marketing communication arena. Working closely with creative direction, copy writing and art direction, interactive design integrates verbal and visual communication along with motion and more importantly, interactivity.

The skill sets in this area are demanding, including knowledge and proficiency of numerous programming languages along with insight into the current Internet browsers that display content. Interactive Design goes beyond web sites to such activities as Web 2.0, blogs, wikis, podcasts, e-communications, search engine optimization, etc.

What challenges most practices is the vast array of interactive opportunities that are available. It isn’t whether or not interactive communications should be part of your plan, but correctly choosing which ones will really make a difference based on your market and your objectives.

Production

This function prepares materials from final art or design and manages the actual creation of a final advertisement, brochure or other produced item. The experience set is unique and requires both a broad and specific knowledge of printing and media mechanics. For example, a simple print ad that is placed in a local newspaper and several magazines requires detailed sizing and an understanding of the different specifications required by each to insure the ad is both placed and printed correctly. When printing a brochure or other collateral pieces, production manages the overall quality of printing by planning how the paper will react to the designated design including cuts, folds, binding and gluing. This function is underrated and misunderstood by most practices because most practices never see this function in action.

Media Planning

Planning media purchases is a series of detailed and complex decisions that determine the most effective tactics to leverage messaging to a designated target audience under a specified budget. Like many of the other planning functions, this requires expertise, good research and experience. Media planners look at geographic coverage, demographics and engagement strengths for each medium and analyze these qualities with such cost efficiency measurements as cost-per-thousand and cost-per-point.

Media planning is an unknown function to many practices. Only a few practices engage in mass media like television or radio advertising and, if they do, will tend to buy packages that are sold by the actual media source. In most cases, media packages are designed for the smallest of businesses because of cost and simplicity, not for effectiveness. Like many efforts practices make, it is rarely the easy ones that produce the most value.

Public Relations

This function is too broad to cover in this article, but in short, public relations manages and orchestrates the perceptions and attitudes of the market for the benefit of the practice. This function can focus on a number of important constituents including the medical community, general community, media, patients and others. Public relations can take the form of events, newsletters, press releases, press conferences and, equally important, assist strategically in times of crisis.

So, what is the most important?

The most important of the above functions is your business strategy. This trumps all others because it sets the direction, the pace, and the available resources. It is inherently a management and physician responsibility and should never be outsourced. This doesn’t mean that consultants with deep and specific expertise shouldn’t provide advice, but only you know your practice’s ambitions and commitment levels.

When it comes to marketing strategy, again, outside experts are valued but only if they provide good research, proven expertise and align their efforts with the previously identified business strategy. Physicians make good decisions when they have good information.

Creative functions (creative direction, design, copy writing, interactive, media planning) are best contracted out to experts. Regardless of the size of your practice, you should always leverage the expertise of those trained, wired and experienced at communications. I understand that most practices deem good design and copy writing expensive, yet the cumulative opportunity cost of not doing it right is significantly more.

In closing, the best marketing is what you do in clinic and in surgery. Everything else is leverage. But when it comes to leveraging your effort correctly, make sure you have a clear vision and then get the right resources focused on achieving it.

Bill Champion is the President of Orthopaedic Marketing Group. Since 1989, Bill has been writing, consulting and speaking on the topics of strategic marketing, business development, practice branding and competitive dynamics. Mr. Champion’s work has been seen in numerous industry publications and through conducting instructional courses at major industry conferences. He can be reached at 402-408-2360 or bchampion@orthopaedicmarketing.com.
KINETIC®-SL Internally Dynamizing Anterior Cervical Plate System

Life Spine received FDA 510(k) clearance for the Kinetic®-SL, a new internally dynamizing anterior cervical plate. This cervical plate system features an integrated lock similar to that of Neo®-SL, which allows bone screws to be securely fixed without any additional locking components. The self-retaining screw capture mechanism is designed to prevent screw rotation and backout while still allowing screw angulation. Like the original Kinetic, Kinetic-SL features 0-2mm of fully adjustable internal dynamization per level. Kinetic-SL also features:

- Ultra slim profile
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- Self-drilling, self-tapping, fixed and variable angle screws
- Pre-lordosed plates in levels 1-5

Life Spine
Tel: 847-884-6117
www.lifespine.com
Enquiry No 25

OtisKnee™ Custom Fit Knee™ Replacement System

Developed by OtisMed Corp., OtisKnee™ total knee replacement technology allows surgeons to customize the size and placement of the knee implant to each individual patient’s anatomy. Unlike “one size fits all” instrumentation, the patientspecific OtisKnee technology was designed to address the fact that everyone’s knees are different. These differences, which can have a tremendous impact on the success of a total knee replacement, may be why nearly 14 percent of total knee replacement patients have reported being either dissatisfied or very dissatisfied with their results after surgery.

The custom-fit OtisKnee approach involves a pre-operative MRI, a proprietary ShapeMatch™ planning process and the production of patient-specific cutting guides. These guides enable surgeons to preserve more bone and ligaments, allowing for better implant fit and alignment. OtisKnee surgeons and patients have reported quicker recovery times, less pain and greater return to function than with traditional and computer-assisted total knee replacement techniques. OtisKnee surgeons have also reported reduced surgical times, simplified surgical set-up as well as quicker patient discharge.


OtisMed Corp.
Tel: 888-OTISMED (684-7633)
www.otismed.com
Enquiry No 26

LYNX™ Cross Connector System

Life Spine recently introduced its Lynx Cross Connector as an addition to its lumbar fixation offering. The innovative design of this system allows for snap-on rod attachment and self-alignment capabilities. With its multi-axial adjustability in all planes and user-friendly design, Lynx allows surgeons more options when presented with a need for a stabilizing cross connector system. Lynx features a variety of lengths via its fenestrated design, with straight and arched versions available in an assortment of adjustable length configurations ranging from 25mm to 100mm. Lockup of the construct at both rods and at the cross connector’s medial joint is accomplished with a single driver tool, which is designed to lock the implant at a predetermined force. The cross connector is designed from surgical grade titanium. Lynx has been designed to be extremely easy and intuitive to use, virtually eliminating the need for bending and requiring only minimal instrumentation.

Life Spine
Tel: 847-884-6117
www.lifespine.com
Enquiry No 27

OrthoWrap Bioresorbable Protective Sheet

The OrthoWrap Bioresorbable Protective Sheet is indicated for the management and protection of tendon injuries in which there has been no substantial loss of tendon tissue. The bioresorbable protective sheet minimizes tissue attachments to the device when in contact with other soft tissues.

OrthoWrap is made from a synthetic polymer of lactic acid 70:30 Poly(L-lactide-co-D, L-lactide), which also forms naturally in the human body. It is well tolerated and elicits no inflammatory response. The film is easy to handle and allows for surgeons to trim it to meet specific anatomical needs. Virtually weightless, the protective sheet is clear and is easy to handle and allows for surgeons to trim it to meet specific anatomical needs. Virtually weightless, the protective sheet is clear and allows for complete visualization of all anatomy for ease of placement.

The OrthoWrap Bioresorbable Sheet is also indicated for reinforcement of soft tissues repaired by suture or suture anchors, during tendon repair surgery, including reinforcement of the flexor or extensor tendons of the fingers, thumb and wrist, rotator cuff, patellar, Achilles, biceps, quadriceps, or other tendons. OrthoWrap reinforces soft tissue and provides a remodelable scaffold that is replaced by the patients own soft tissue.

MAST Biosurgery, Inc.
Tel: 866-627-8246
www.mastbio.com
Enquiry No 28
**SpF® PLUS-Mini Spinal Fusion Stimulator**

Biomet Spine has introduced the SpF® PLUS-Mini Spinal Fusion Stimulator to address the demand for a proven option to enhance posterolateral fusion success rates. This is the next generation of implantable SpF devices that have proven to be a safe, cost-effective adjunct for spinal fusions since 1987, backed by over 30 published scientific and clinical papers showing long-term success.

The direct current technology at the heart of the SpF PLUS-Mini stimulator involves the upregulation of BMPs (Bone Morphogenetic Proteins) and other growth factors, including BMP 2, 6 and 7 and the BMP receptor ALK2, which are normal physiological regulators of various stages of bone healing, including chondrogenesis and osteogenesis. The SpF PLUS-Mini stimulator has shown a 50% increase in success rates over autograft alone. In addition, the SpF PLUS-Mini stimulator features a 67% smaller generator than the original SpF®-PLUS device with a slimmer, lower-profile design for enhanced patient comfort while still providing 60 microamps of direct current stimulation. Because the SpF PLUS-Mini stimulator is implanted, it can offer continuous treatment without patient compliance issues, which is especially important during the crucial first six months of treatment.


**VertiGraft VG1® Cervical Allograft Bio-implant**

The new VertiGraft VG1® Cervical allograft bio-implant is engineered for use in anterior cervical fusion (ACF) surgery to address cervical pathologies. The VG1 Cervical bio-implant’s one-piece cortical construction and textured surface area provide the critical strength and stability required by an implant in this application. The VG1 Cervical bio-implant’s chamfered profile, as well as specifically-designed insertion instrumentation, are intended to ensure easy graft implantation.

The VG1 Cervical bio-implant is freeze-dried, allowing the convenience of maintaining this product at room temperature without the hassle of freezer storage. The bio-implant is processed with LifeNet Health’s proprietary and patented Allowash XG® technology. Since 1995, LifeNet Health has distributed 1.8 million bio-implants with no incidence of disease transmission linked to tissue screened and processed using Allowash XG.

The VG1 Cervical bio-implant is co-developed by LifeNet Health and DePuy Spine and is exclusively represented in the U.S. by DePuy Spine.

**STATURE™ Vertebral Body Replacement System**

The STATURE VBR System by Atlas Spine is a radiolucent self-distracting spacer designed to meet the most challenging demands of the spine surgeon. The system’s proprietary instruments and unique implant geometry provide a simple, controlled method for restoring the natural anatomical height and sagittal balance to severely compromised spaces.

The STATURE system is complemented by the BACK-PAK™ DS, Atlas Spine’s comprehensive disc preparation set. MIS compatible, the system is designed to maximize proficiency and provide the optimum weight, balance and feel for the surgeon. The BACK-PAK DS supports the philosophy that an efficient and successful surgery is significantly impacted by less invasive instrumentation and techniques as well as the implants themselves.

Manufactured from PEEK Optima®, STATURE implants are available in lordotic and non-lordotic options ranging in 9 - 17mm heights. STATURE™ and BACK-PAK™ are trademarks of Atlas Spine, Inc. Optima® is a registered trademark of Invibio.
The path to becoming an orthopaedic surgeon is long and arduous. After completion of medical school and residency, most surgeons look forward to beginning the “practice” of orthopaedic surgery. In reality, that practice is not something that simply begins on the day after completion of residency or even after passage of orthopaedic board examinations. The practice is actually a continuum of learning and skill acquisition that will take the young surgeon on a journey for the next 30 or 40 years. During this time, the practice itself will change with respect to demands on resources and organizational support in ways never imagined by the young surgeon.

The career of an orthopaedic surgeon comprises three main phases. Understanding these phases gives insight into the surgeon’s changing needs regarding practice support. The first phase, occurring shortly after graduation from residency, is that of the acquisition of knowledge. Although most orthopaedic surgeons feel that at the completion of their chief resident year they are able to handle any orthopaedic problem with ease, the reality soon sets in that orthopaedic skill is an acquired one, and truly develops over time. It takes approximately ten years for an orthopaedic surgeon to develop all of the skill sets to be an accomplished practicing surgeon. During that time it is very important that the surgeon see and participate in as many different case situations as possible. During this early career, the acquisition of knowledge should be the surgeon’s primary motivating force. During this phase there runs a parallel path of knowledge acquisition in the development of the business of being an orthopaedic surgeon. Surgeons learn very little about developing and managing a surgical practice during residency. The surgeon will look for outside help in billing, electronic health records, buying into a practice or building one from the ground up. During this time many surgeons change their practice situation, dealing with contractual and financial issues as they seek a good fit to establishing a permanent practice.

The second phase, which typically begins ten or so years following completion of residency, is one of practice development. Surgeons today are faced with a dilemma of joining an established orthopaedic practice, staying on staff with an academic faculty or building their own practices. Each situation has advantages and disadvantages. Most surgeons in private practice typically face the challenge of developing a patient and referral base that will be loyal to and supportive of their practice over the years. It is during this second phase of professional development that the practice starts to build for those surgeons who have either gone into their own practice or joined a small group practice. During this phase, it becomes clear that the greatest referral source is a successful patient who acts as the ultimate marketer. Conventional modalities of building practice volume, including advertising, directed marketing and so on, pale compared to the power of a successful and happy patient who tells other patients about the surgeon. During this phase, the surgeon will make business choices including whether to contract with payers or to focus on a patient-centered approach devoid of contracts. The business side of the practice development phase is dominated by cost control strategies and expansion of business opportunities. During this phase, the surgeon may decide to develop a surgery center, move to digital radiography or take in a younger partner to build the practice’s financial base. The surgeon will need access to capital to help fuel this growth. On the cost control side, the surgeon may look to develop a more efficient billing system, implement a credit card strategy to collect fees, or find less expensive record storage options.

The third phase of professional development for an orthopaedic surgeon begins approximately 15 to 20 years after graduation from the residency program, when the surgeon has had a stable and thriving practice and is now more concerned more about wealth preservation and providing for the future. Now the surgeon may look for help on retirement planning or potentially embarking upon a professional life beyond the practice. Most surgeons do not simply turn away from the practice of orthopaedic surgery and retire. The true orthopaedic professional understands that being an orthopaedic surgeon is really much more about who they are and not just what they do. This time can be very rewarding and fulfilling.

The three phases of orthopaedic professional development occur after residency and are consistent and inevitable. The business demands of the surgeon change during this path of professional development and are predictable. The practice of orthopaedic surgery, although challenging, is incredibly rewarding and allows for a lifetime of knowledge acquisition and service.

Tom Grogan is a pediatric surgeon from Santa Monica, California and a co-founder of Ortho Practice Solutions (OPS), a financial and educational services company dedicated to orthopaedic surgeons. OPS can be contacted at 888-678-4694. Dr. Grogan can be reached at info@orthopracticesolutions.com.

Please feel free to contact OPS directly by faxing the following contact form.

Enquiry No 32
Ortho Practice Solutions
6230 California St. San Francisco, CA 94121
Phone: 888-678-4694 Facsimile: 415-631-4749
info@OrthoPracticeSolutions.com
www.OrthoPracticeSolutions.com

Name ________________________________
Practice address ________________________________
_________________________________________________

Phone number ________________________________
Contact name at the office ________________________________
E-mail address ________________________________
_________________________________________________

Type of Practice:  ○ solo    ○ group

I am interested now in receiving information on these products:

○ Disability Insurance    ○ Liability insurance
○ Other insurance    ○ Surgery Centers
○ Equipment Leasing    ○ Debt Consolidation
○ Working Capital    ○ Selling or buying used equipment
○ New equipment    ○ Practice management tools
○ Mortgages    ○ Automobiles
○ Pensions    ○ Patient Financing
○ MRI Interpretations    ○ Reorganization of Surgery Centers

Within the next year I will be interested in receiving information on these products:

○ Disability Insurance    ○ Liability insurance
○ Other insurance    ○ Surgery Centers
○ Equipment Leasing    ○ Debt Consolidation
○ Working Capital    ○ Selling or buying used equipment
○ New equipment    ○ Practice management tools
○ Mortgages    ○ Automobiles
○ Pensions    ○ Patient Financing
○ MRI Interpretations    ○ Reorganization of Surgery Centers
Emerging Orthopaedic Technologies & Treatments

Recent FDA Clearances
February and March 2008

<table>
<thead>
<tr>
<th>ACCIN Patellofemoral Screw System</th>
<th>ACCIN Pedicle Screw System</th>
<th>(ACCELERATED INNOVATION)</th>
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<tbody>
<tr>
<td>BioFlex Pedicle Screw System</td>
<td>(BIOSPINE)</td>
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<tr>
<td>AperFix Interference Screw</td>
<td>(CAYENNE MEDICAL)</td>
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<tr>
<td>Oria Natura Spacer</td>
<td>(CHOICESPINE)</td>
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<tr>
<td>Extended Articulation Humeral Head</td>
<td>(DVO EXTREMITY SOLUTIONS)</td>
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<tr>
<td>Suture Lock Bone Screw Anchor</td>
<td>(KFX MEDICAL)</td>
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<tr>
<td>BCP Bone Void Filler</td>
<td>(GRAFTYS)</td>
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<td>Spinal Sphere System</td>
<td>(LIFE SPINE)</td>
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<tr>
<td>Total Hip System Quadra S + C, MedCaCer BIOLOX</td>
<td>(MEDACTA)</td>
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<td>Forte Femoral Heads</td>
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<td>K-Phate Bone Graft Substitute</td>
<td>(MERRIES INTERNATIONAL)</td>
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<td>Savannah Lumbar Percutaneous Stabilization System</td>
<td>(NEUROSPINE INNOVATIONS AND SOLUTIONS)</td>
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<td>Modular Foot System</td>
<td>(ORTHOPEDIATRICS)</td>
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<td>Plating System</td>
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<td>DC Ulnar Shortening System</td>
<td>(ORTHOPRO)</td>
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<tr>
<td>Plexur P and Plexur M Bone Void Fillers</td>
<td>(OSTEOTECH)</td>
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<td>Buttress Washer System</td>
<td>(RELIANCE MEDICAL SYSTEMS)</td>
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<td>Nails and Pins</td>
<td>(SANATMETAL)</td>
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<tr>
<td>Kimba Mini Vertebral Body Replacement</td>
<td>(SIGNUS)</td>
<td></td>
</tr>
<tr>
<td>TwinFix PK FP Suture Anchor</td>
<td>(SMITH &amp; NEPHEW)</td>
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<td>EnsplintRx Bone Fixation System</td>
<td>(SONOMA ORTHOPEDIC PRODUCTS)</td>
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<td>Indus Anterior Cervical Plate System</td>
<td>(SPINEFRONTIER)</td>
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<td>Cimplicity Spinal System</td>
<td>(SPINESMITH PARTNERS)</td>
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<tr>
<td>Unicompartmental Knee</td>
<td>(VALPO ORTHOPEDIC TECHNOLOGY)</td>
<td></td>
</tr>
<tr>
<td>FDA 510(k) Releasable Database</td>
<td>2/08 and 3/08</td>
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</table>

TranS1 noted that a reimbursement coding committee will propose a separate Category III tracking code for translumbar fusion. The code would allow TranS1 to collect data in support of a Category I reimbursement code for the procedure by 2009. If successful, the code could become effective in 2010. (Form 8-K, TranS1 Inc., SEC.gov, 2/19/08)

A third round of results from the Spine Patient Outcomes Research Trial (SPORT) revealed that surgical treatment of spinal stenosis yielded more rapid improvement and better physical function, as well as less pain, vs. non-surgical treatment, though patients who declined surgery were likely to improve over time. Future trial results will address cost-effectiveness and other measures. (Dartmouth College, 2/20/08)

SonoSite introduced S-MSK™, a handheld ultrasound tool customized for musculoskeletal specialists. S-MSK technology acquires an optimal image using only two controls, and can be utilized for superficial and deep assessments, guidance of injections and aspirations of the knee, shoulder, elbow, etc. (SonoSite, Inc., 2/22/08)

The World Health Organization is funding a web-based tool called FRAX that calculates the likelihood of a hip, wrist, shoulder or spine fracture within the next ten years for anyone aged 40 or older in nine different countries. (AP Medical, 2/25/08)

Researchers are investigating use of an unusually pliant and strong synthetic hydrogel that may function as a cartilage replacement. The material reportedly won’t break apart even when deformed over 1,000%. (National Institute of Standards and Technology, 3/10/08)

Study results suggest that patients who underwent arthroscopic surgery to treat 1st-time shoulder dislocations maintained excellent use of the affected joint at 11+ years and, on average, reported function at 93% of pre-injury levels. (HealthDay News, 3/10/08)

Researchers in New Zealand are investigating biomimetic intervertebral disc replacements for use as a clinical alternative to spinal fusion. The team is studying polymers and novel solvents in combination with processing methods such as electrospinning to produce nanofibers that may recreate disc properties. (The Engineer Online, 3/13/08)

ArthroCare launched a fully operational, five station Mobile Surgical Skills Center for sports medicine-related surgical training and physician education in the U.S. (ArthroCare Corp., 3/13/08)

Results from mechanical testing suggest that Titan Spine’s Titanium Vertebral Body Replacement, ENDOSKELETON™ TA, performed “exceptionally well” with respect to pull-out strength. The device was compared to a variety of others in materials including PEEK, allograft bone implants and titanium threaded fusion devices. (Titan Spine, LLC, 3/18/08)

Results from a 5-year follow-up study of 884 osteoporosis patients suggest that vertebroplasty provides dramatic pain relief and sustained benefit, and that the procedure does not increase the risk of fracture in nearby vertebra. The average pre-treatment pain score on the 11-point Visual Analog Scale was 7.9 +/- 1.5, and it dropped significantly to an average of 1.3 +/- 1.8 after the vertebroplasty treatment. Abstract 182, “Percutaneous Vertebroplasty in the Osteoporotic Patients: Five Years Prospective Follow-up in 884 Consecutive Patients,” can be found at www.SIRmeeting.org. (Society of Interventional Radiology, 3/19/08)

LDR completed enrollment for a U.S. 2-level Investigational Device Exemption study of the 2nd-generation Mobi-C® cervical disc. The device has been used to treat >5,500 patients worldwide, including 600 patients involved in this study. (LDR, 3/24/08)
### Ticker Track (Based on close of business, 3/31/08)

<table>
<thead>
<tr>
<th>Company</th>
<th>Symbol</th>
<th>52-Wk High</th>
<th>52-Wk Low</th>
<th>Close</th>
<th>Chg vs. Prior Mo.</th>
<th>Chg vs. Prior Yr.</th>
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<td>aap †</td>
<td>AAQ</td>
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<td>3.09</td>
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<td>Alphatec Holdings</td>
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<td>co.don AG †</td>
<td>CNW</td>
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<td>ConMed</td>
<td>CNMD</td>
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<td>Corin Group ††</td>
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<td>curasan †</td>
<td>CUR</td>
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<td>Inion ††</td>
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<tr>
<td>Japan ‡</td>
<td>7600</td>
<td>2.93</td>
<td>2.08</td>
<td>2.46</td>
<td>0.8%</td>
<td>-4.3%</td>
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<td>MAKO Surgical</td>
<td>MAKO</td>
<td>11.99</td>
<td>8.36</td>
<td>8.99</td>
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<td>NuVasive</td>
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<td>45.3%</td>
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<td>-22.1%</td>
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<td>OLGC</td>
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<td>0.85</td>
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<td>-45.5%</td>
</tr>
<tr>
<td>Orthovita</td>
<td>VITA</td>
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<td>-11.6%</td>
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<td>Osiris Therapeutics</td>
<td>OSIR</td>
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<td>9.98</td>
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<td>22.5%</td>
<td>-32.8%</td>
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<tr>
<td>Osteotech</td>
<td>OSTE</td>
<td>8.70</td>
<td>4.12</td>
<td>4.75</td>
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<td>-37.8%</td>
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<td>RGBI</td>
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<td>0.04</td>
<td>0.15</td>
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<td>-70.0%</td>
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<td>RTI Biologics</td>
<td>RTIX</td>
<td>11.99</td>
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<td>30.3%</td>
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<td>Smith &amp; Nephew</td>
<td>SNN</td>
<td>68.48</td>
<td>54.08</td>
<td>55.99</td>
<td>9.9%</td>
<td>4.0%</td>
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<tr>
<td>Stryker</td>
<td>SYK</td>
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<td>58.45</td>
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<td>Symmetry Medical</td>
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<tr>
<td>Synthes †</td>
<td>SYST</td>
<td>158.64</td>
<td>124.00</td>
<td>142.47</td>
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<tr>
<td>TranS1</td>
<td>TSON</td>
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<td>11.65</td>
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<td>Wright Medical Group</td>
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†Converted from Euro to USD; 1€ = 1.5715 USD.
††Converted from British Pound to USD; 1£ = 1.9919 USD.
‡Converted from Swiss Franc to USD, 1CHF = 0.9922 USD.
§Converted from Yen to USD, 1¥ = 0.0098 USD.

In order for a company to qualify for inclusion in the OrthoInvestor Update, orthopaedics must represent at least 60% of its revenues.

### Company Financials

#### 2007 vs 2006

<table>
<thead>
<tr>
<th>Company</th>
<th>Sales (MM) vs. Prior</th>
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<tr>
<td>Alphatec</td>
<td>$80.0 +8%</td>
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<tr>
<td>ArthroCare</td>
<td>$234.2 +24%</td>
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<td>Smith Nephew</td>
<td>$189.6 +14%</td>
</tr>
<tr>
<td>ConMed</td>
<td>$413.8 +10%</td>
</tr>
<tr>
<td>NuVasive</td>
<td>$264.5 +13%</td>
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<td>Exactech</td>
<td>$124.2 +21%</td>
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<tr>
<td>Orthofix</td>
<td>$442.6 +38%</td>
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<tr>
<td>NuVasive</td>
<td>$154.0 +57%</td>
</tr>
<tr>
<td>Orthofix</td>
<td>$424.3 +68%</td>
</tr>
<tr>
<td>Smith Nephew</td>
<td>$111.9 +17%</td>
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<tr>
<td>Osteotech</td>
<td>$87.5 +11%</td>
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<td>Ostimed</td>
<td>$104.3 +5%</td>
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<tr>
<td>DBM</td>
<td>$65.8 +14%</td>
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<td>OrthoMed</td>
<td>$18.8 +39%</td>
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<tr>
<td>Spinal Allograft</td>
<td>$10.7 +22%</td>
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<tr>
<td>Smith &amp; Nephew</td>
<td>$7.6 +17%</td>
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<tr>
<td>Other</td>
<td>$0.7 +23%</td>
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<tr>
<td>Smith &amp; Nephew</td>
<td>$2,590.0 +15%</td>
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<tr>
<td>Fixation</td>
<td>$469.0 +21%</td>
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<tr>
<td>Biologicals</td>
<td>$568.0 +9%</td>
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<tr>
<td>Clinical Therapies</td>
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<tr>
<td>Other</td>
<td>$125.6 +21%</td>
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<tr>
<td>Smith &amp; Nephew</td>
<td>$2,759.7 +13%</td>
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<td>Other</td>
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<td>$62.3 +37%</td>
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<tr>
<td>OrthoMed</td>
<td>$104.3 +5%</td>
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</tbody>
</table>

†Orthopaedic product sales only.
Constant currency

Company news releases, 2/08
Does U.S. Recession Mean Ortho Regression?

As the U.S. economy seems to be hurting with ever greater certainty into recession (if we are not already in the middle of one), our clients have been asking whether to expect orthopaedics to go down with the rest of the ship.

The reflexive, and maybe most intuitive, answer is “no.” The demand for orthopaedic procedures is not economically driven. An arthritic hip is not so courteous as to wait for the unemployment index to drop below a certain threshold before requiring treatment. People come in for surgery when the pain of postponing has become too much to bear, which has nothing to do with what the broader economy is doing.

Of course, there are myriad variables that could throw this intuitive answer off. Do hospitals push back harder on price when the economic outlook seems grim? Does higher unemployment cause a decrease in procedure volume as patients lose insurance coverage?

A more rigorous analysis of the relationship between growth in the orthopaedic industry and the broader economy may be instructive. For the purposes of this discussion, we will focus on U.S. hips and knees, the largest market in orthopaedics, and the driver of growth at most of the large orthopaedic companies. We focus on Real GDP as the indicator of activity in the broader economy, which declines during a recession.

The last recession in the U.S., as determined by the National Bureau of Economic Research, lasted from March 2001 through November 2001. Exhibit 1, below, charts total year-on-year growth in U.S. hips and knees in comparison to year-on-year growth in Real GDP.

This chart tells us a few things. First, U.S. hip and knee growth actually accelerated through the last recession in the U.S. In fact, during the 18 months from 2Q00 through 4Q01, when GDP steadily decelerated from 4.8% to 0.2%, hips and knees steadily accelerated from 7.7% to 22.4%. In short, GDP growth and orthopaedic growth showed an inverse correlation during the last recession.

At other times, changes in GDP growth appear to have had a direct relationship with hip and knee growth. From 1Q03 through 1Q05, GDP and hips and knees followed a relatively similar pattern in changes in growth, though the magnitude of change was very different. Interestingly, during this period, changes in hip and knee growth actually preceded changes in GDP growth by a quarter.

After 1Q05, the two diverged again; hips and knees decelerated from 2Q05 through 1Q06 while GDP was relatively flat, and then accelerated from 2Q06 through the present, when GDP was flat or decelerating.

For the total period shown, growth in the hip and knee market shows a correlation with GDP of -0.17; p=0.36, i.e. a weak inverse correlation, not reaching statistical significance.

The takeaway is that despite periods of some apparent correlation, Real GDP and the hip and knee market have not shown a consistent direct relationship, and have in fact more often than not moved in opposite directions. The implication for the question we posed at the beginning of this piece is that a decline in GDP (i.e. a recession) cannot...
be shown by historical example to lead to a decline in growth for the orthopaedic industry.

But our analysis cannot be complete without attempting to understand the drivers of growth. In other words, we need to understand why growth is changing. Throughout the entire period shown in Exhibit 1, unit volume was relatively stable, in the mid-to-high single digits, while total growth swung from six percent in 1Q00, to 21% in 1Q04, and then back down to five percent by 1Q06.

The swing factor is price. In our analysis of the orthopaedic industry, we focus on price as the most important driver of market growth, simply because it is the largest moving part. If you can predict changes in price, you can predict changes in total growth for the market.

The price the big companies receive for their products is directly related to the global price hospitals receive from payors for hospital services. Hospitals tend to fund less profitable procedures with funds from other areas of the hospital in order to meet volume demands. As prices of orthopaedic devices rise, and orthopaedic procedures necessarily become less profitable, the hospital’s ability to draw funds from other areas determines whether prices can continue to rise. For this reason, total pricing in the hospital, an indicator of the financial health of the hospital as a whole, is most important to orthopaedic pricing. Reimbursement for orthopaedic procedures is (perhaps surprisingly) not much of a driver at all. So long as hospitals are able to pass higher prices on to payors, they will be less sensitive to changes in the price of orthopaedic devices.

We follow hospitals’ ability to pass on price by looking at Hospital CPI (technically, Hospital and Related Services CPI), a government number. Exhibit 2, below, demonstrates the relationship of Hospital CPI, hip and knee price, and Real GDP.

Exhibit 2, which contains historical data going back all the way to 1988, shows hip and knee price (the red dots) next to Real GDP (the purple dashed line) and Hospital CPI (the blue solid line). The chart shows a positive correlation between Hospital CPI and orthopaedic price, with inflections in Hospital CPI generally leading inflections in hip and knee price by about a year. There is no correlation between orthopaedic price and Real GDP, and interestingly, Hospital CPI and GDP are actually inversely correlated.

Similar to our first exercise, this second analysis shows no consistent relationship between GDP and orthopaedic pricing, the driver of growth in the U.S. market. In fact, Hospital CPI, a leading indicator of the true driver or orthopaedic pricing (and therefore total growth) has historically expanded while GDP (and the broader economy) has been in decline.

The conclusion from both of these analyses is that GDP and growth in the core hip and knee market are not related. In other words, the fact that the economy may be headed into a recession should have little bearing on the trajectory of growth for orthopaedics. In fact, Hospital CPI has been in a sustained uptrend since late 2005, which means that orthopaedic growth should be set for at least another year of expansion if not longer.

What could cause our outlook to be wrong? If the recession we are headed into turns out to be unusually severe and a large number of people end up unemployed, uninsured and unable to afford surgery, procedure volume would likely drop. Another wildcard is the political cycle. The cost of healthcare is a big issue on the campaign trail, and all three candidates have a plan for how to revamp our system. Increased involvement by the government in the determination of price would undoubtedly have a detrimental impact on the industry. Finally, if in an effort to control ballooning Medicare/Medicaid budgets, state and/or Federal governments begin to significantly cut payments to hospitals, our pricing thesis would be directly impacted, and the orthopaedic industry (along with the rest of healthcare) would suffer. CMS proposed a three percent payment update to hospitals for the 2009 fiscal year, so cuts would be unlikely before 2010.

These are issues which could affect the industry a year or more from today. Major politically driven changes in particular are unlikely to materialize anytime soon. For the near term, and assuming that historical trends hold (of which there is, of course, no guarantee), the hip and knee market should continue on track. We expect continued expansion in the space, and have Overweight ratings on all of the orthopaedic stocks under our coverage.

Philip Legendy covers Medical Devices in the Healthcare group at Thomas Weisel Partners. He has been with Thomas Weisel Partners since 2006, and has been covering the Medical Device sector, including large-cap orthopaedics, for the past five years. Philip’s current coverage includes Stryker, Zimmer, Wright Medical Group and NuVasive, among other names in the Medical Device space. Prior to joining Thomas Weisel Partners, Philip covered the space as a research associate at JMP Securities and Prudential Equity Group. Philip received a B.A. in Political Economy from Princeton University. For more information, contact plegendy@weisel.com.
Anthony Viscogliosi
Chairman & CEO,
Small Bone Innovations, Inc.

Anthony G. Viscogliosi is the Chairman and Chief Executive Officer of Small Bone Innovations, Inc. (SBI). He was instrumental in the research, development and funding of SBI, along with his brothers John and Marc. SBI’s mission is to be the single-source provider of innovation, products and technology for orthopaedic surgeons treating bones and joints from the fingers to the shoulder, and from the toes to below the knee.

Founded in 2004, SBI has more than 130 employees in the U.S. and France. It also has accumulated more than 60 product systems via acquisitions, licensing and in-house development.

U.S. Orthopaedic Product News recently spoke with Mr. Viscogliosi regarding the company’s orthobiologics portfolio.

*U.S. Orthopaedic Product News (OPN): Using Artelon® as the example, where do orthobiologics fit into the SBI business strategy?*

**Anthony Viscogliosi (AV):** If history repeats itself, as it has in hips, knees and spine, by moving from fusion to non-fusion – or what I call radical therapies to conservative ones – treatment of osteoarthritis (OA) in the thumb, fingers and wrist will emphasize conservation rather than removal of tissue. This is uniquely reflected in the Artelon program.

**OPN:** Please elaborate on this.

**AV:** In the four classic stages of joint treatment - removal, repair, replacement and regeneration - orthobiologic materials, such as Artelon, have the ability to support new tissue growth and can eliminate the need to harvest tissue from elsewhere in the body. This represents a conservative alternative to ligament reconstruction tendon interposition (LRTI) and fusion procedures, which are still widely performed in thumb repair.

**OPN:** What level of acceptance has the Artelon Spacer experienced to date?

**AV:** We estimate that there are at least 5,000 patients with Artelon implants worldwide. The Artelon CMC Spacer was originally cleared by FDA in 2004 to be used as an interpositional spacer between the trapezial and first metacarpal bones – for patients with thumb disabilities caused by OA. Since then, the product line has been augmented to include products for arthroscopic implantation such as the Artelon CMC Spacer Arthro and the Artelon Spacer STT for the scapho-trapezio-trapezoidal joint.

**OPN:** What has been the typical experience for those with Artelon implants?

**AV:** Initial outcomes have been very positive. Clinical studies and anecdotal feedback from surgeons and patients indicate that patients benefit from the relief of OA pain and significantly improved pinch strength – which is the ability to oppose your fingers as in holding a key or glass. Patients are obviously happy with a less invasive alternative to the LRTI procedure that requires resection of the trapezial bone, combined with the sacrifice of tissue harvested from the forearm.

**OPN:** Exactly what stage in the progress of OA is suitable for this procedure?

**AV:** Artelon usually offers patients a less radical surgical alternative in the early- to mid-stages of disease progression. Artelon tends to work best for those patients with OA defined as late Eaton Stage I through early Stage III. These patients will have failed non-surgical therapy such as NSAIDs, splinting and corticosteroid injections. Patients who exhibit signs of pan-trapezial disease (STT joint involvement) tend to benefit less from the Artelon CMC Spacer. This fact led us to develop the Artelon STT Spacer for that joint.

---

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Enquiry No 7
EXECUTIVE INTERVIEW

continued from page 22

OPN: What is the recommended post-operative recovery protocol for Artelon patients?

AV: The thumb must be immobilized in a cast for five to six weeks and any strenuous activity or lifting heavy weights should be avoided for 12 weeks, post-op. Pain, redness and swelling can sometimes appear in patients who try to return to normal activities too soon.

OPN: If it takes at least six years for the body to resorb degradable material, are there fluctuations in pain, swelling or joint dysfunction as the material degrades?

AV: While there have been occasional reports of soft tissue irritation, possibly due to movement of the implant or fixation devices, most patients do not report discomfort or pain. During the degradation period, tissue begins to reform around the Artelon scaffold.

In vitro tests have shown that Artelon retains about 50 percent of its original tensile strength after four years. After six years about 50 percent of the original mass remains at the implant site following degradation, while the rest of the material is resorbed into the host tissue.

Exhibit 1, below, shows a light micrograph from one patient with an Artelon CMC Spacer 12 months after implantation. Artelon (A) is stained turquoise and is surrounded by connective tissue with fibroblasts (Fb). The interface between Artelon and connective tissue (I) shows no sign of foreign-body reaction.

Exhibit 1: Light micrograph of the interposition portion from one patient with an Artelon CMC Spacer 12 months after implantation shows Artelon (A) is surrounded by connective tissue. (Bar=100µ m.)

Further, in Exhibit 1, biopsies from the vertical interposition part of the spacer reveal ingrowth of fibrocartilage in the spacer and a completely irritation free interface between biomaterial and surrounding host tissue.

OPN: Are any other studies underway that will provide data on patient outcomes with Artelon?

AV: In addition to the study I just mentioned, the same patient set continues to be followed and Artimplant, the Swedish developer of Artelon, is planning a more extensive analysis, including x-rays, histology, etc., when the six-year data becomes available.

Other studies that are currently underway include a U.S. multi-center retrospective study with six surgeons and 73 patients.

OPN: What do you believe are the pros and cons of Artelon compared with LRTI and arthrodesis or any other thumb joint surgical procedures?

AV: Anecdotally, surgeons have observed the following "pros" of Artelon, in no particular order of importance – but obviously each of these is significant:

Pros:
• It is a less invasive, tissue preserving alternative. There is no trapeziectomy or tendon harvesting, thus preserving the essential anatomy of the hand and wrist.
• Artelon patients exhibit clinically significant increases in key pinch and tripod pinch strength, while experiencing pain relief and range of motion comparable to LRTI.
• Early restoration of form and function.
• Long term reduction of pain comparable to LRTI.
• Artelon may be suitable for a broader range of patients, especially those in earlier stages of disease development. It burns no bridges and leaves open the option to perform an LRTI at a later stage, if necessary.
• Artelon is a relatively simple surgical procedure able to be performed under regional anesthesia. It can also be implanted arthroscopically. Patients can resume many routine, non-stressful activities within six weeks and return to unrestricted use, within reason, after about 12 weeks.

continued on page 25

1 Artelon Preclinical Data, Results of Animal, Human Safety & Implantation Work, Artimplant AB, Vastra Frolunda, Sweden.
Artelon can increase the lost joint space while providing additional stability to the diseased joint.

**Cons:**
- The Artelon CMC Spacer is not appropriate for treating patients with advanced (later stage) disease or involvement of the STT joint (although we now have a spacer for that condition, the Artelon STT Spacer).
- As with any “new” procedure, patient selection is critically important, so Artelon is not an “automatic” substitute for LRTI or even non-surgical procedures.
- Patients who do not carefully follow the post-operative recovery protocol recommended in the IFU can develop pain or swelling.
- Prematurely stressful activity could disrupt the healing process supported by the spacer with the surrounding tissue.
- The early relief of pain and a sense of “healing” sometimes results in patients ignoring post-operative recovery protocols – with potentially harmful consequences.
- The spacers are not designed to provide lateral stability.

**OPN:** Although Artelon is still in its infancy, so to speak, do you foresee wider adoption by surgeons?

**AV:** The orthopaedics market as a whole, and the small bone and joint market specifically, are being driven by three factors that SBi and the medical profession have recognized that will impact the prospects for Artelon and most other devices that offer comparable benefits:

1. The human physique is not built to last as long as we are living – or want to live – without becoming disabled.
2. The disproportionate growth in the number of “older people” in the world population suggests that orthopaedic devices will proliferate, none faster than those for small bones and joint treatment – almost half of all orthopaedist OVs involve the extremities.
3. People are working longer and are determined to remain active by demanding the preservation or restoration of physical function and motion – as the volume growth in hip and knee replacement, for example, amply demonstrates.

**OPN:** Are there sufficient numbers of surgeons able to meet the kind of demand this suggests and who will pay for these new treatments?

**AV:** According to the 2007 AAOS Orthopedic Physician Census, 49 percent of all U.S. Fellowships in orthopaedics cover the small bone and joint anatomies. In addition to the 2,800 or so hand surgeons in the U.S., a great many other orthopaedists are capable of performing Artelon implants. Also, this procedure is reimbursed by many private health insurers and SBi has submitted an application to receive a pass through code from CMS. Because the Artelon Spacer procedure is so much less invasive than more radical procedures like LRTI, both patients and insurers will benefit if wider reimbursement is approved.

**OPN:** Finally, what are your plans for expanding the range of Artelon applications in the U.S.?

**AV:** Late last year we signed a new licensing agreement with Artimplant AB, the developer and patent holder of Artelon, based in Vastra Frolunda, Sweden. The agreement addresses potentially all future resurfacing and interposition applications of Artelon technology in the fingers, hand and wrist domain.

This is in addition to the four FDA-cleared applications for arthritic thumb repair we currently offer. The agreement covers the entire global market with the exception of the Nordic countries.

Artelon® is a registered trademark of Artimplant AB.

Exhibits from this article, as well as the Artelon Biodegradation Leaflet, are available at www.totalsmallbone.com. For more information, please contact customerservice@totalsmallbone.com.
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Joseph Borrelli, Jr, MD  UT Southwestern Medical Center - Dallas, TX

“PRO-DENSE® Graft is the ideal product in situations of bone loss. The unique calcium sulfate and calcium phosphate combination allows the graft to be absorbed at an ideal rate as it is being replaced by bone.”
Raffy Mirzayan, MD  Saint Barabara's - Los Angeles, CA

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William M. Ricci, MD  Brigham University - Salt Lake, UT
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Zeta Potential Control (ZPC™)

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Enquiry No 37

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Harvest manufactures the SmartPReP® Bone Marrow Aspirate Concentrate (BMAC™) System. The SmartPReP BMAC System is the first technology that rapidly concentrates clinically significant amounts of stem and precursor cells from a small aspirate of autologous bone marrow at patient point-of-care.

Before SmartPReP, processing and concentrating a clinically significant dose of adult stem cells from a patient’s bone marrow was difficult and time consuming. With SmartPReP, as little as 60-120 ml of bone marrow aspirate can be concentrated at point-of-care in just 15 minutes. The SmartPReP BMAC System has been documented to effectively and reproducibly collect mononuclear cells in concentrations up to 7 times native levels while maintaining the viability and function of the cellular components. With minimal processing time, concentrated autologous adult stem cells can be available to the clinician as needed at patient point-of-care.

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Enquiry No 36

Xybrex Anesthetic Matrix

ORTHOCON’s lead product, Xybrex Anesthetic Matrix, provides local pain management and bone hemostasis. During most orthopaedic procedures, surgeons will cut or drill into bone, causing bleeding and damaging nerves that reside in and around the bone, a source of severe pain. Xybrex Matrix is applied to these sites during the procedure to stop bone bleeding. Once implanted, Xybrex Matrix begins to release effective amounts of a local anesthetic over a prescribed period of time, e.g., three days. After a period of effective pain relief is achieved, the Xybrex Matrix will safely and completely absorb, requiring no postoperative physician or nurse intervention.

Xybrex Matrix has a putty-like consistency and is designed to adhere to bone. Xybrex products are ready to use out of the package and do not swell after application. Since the medication is designed to be used locally, greater amounts of active drug can be administered directly to the origin of the pain than could be dosed to the site systemically.

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Enquiry No 38
AlloFuse® and AlloFuse Plus®

AlloFuse® products reportedly have one of the highest demineralized bone matrix (DBM) contents available and are designed to help stimulate natural bone formation processes in which mesenchymal cells differentiate into bone-forming cells. Used either alone or as a bone graft extender, AlloFuse® products are intended to promote successful surgical outcomes by providing:

- Proven osteoinductivity
- Superior handling
- Excellent graft containment
- Ready-to-use application

AlloFuse® Plus combines the capabilities of AlloFuse® with the osteoconductive properties of cancellous bone. In one product surgeons now can have osteoinductivity and osteoconductivity. AlloFuse® Plus has a unique temperature-responsive medium that facilitates both handling and graft containment. AlloFuse® Plus benefits include:

- The DBM provides the osteoinductive signal to form new bone
- The cancellous bone supplies an osteoconductive scaffold facilitating the attachment of osteogenic precursor cells.

Artelon® Bioabsorbable Spacers

Artelon® CMC Spacer is designed as a conservative, tissue preserving option for the treatment of early stage CMC joint arthritis. The Artelon® CMC Spacer is CE-Marked, FDA cleared and marketed globally by Small Bone Innovations.

Artelon Spacers provide a particularly attractive option for patients at the early- to mid-stages of disease development. Patients suffering from CMC OA are often not appropriate candidates for more radical alternatives like trapeziectomy or joint fusion. The Artelon Spacer family consists of four products geared to treatment of thumb based osteoarthritics at different stages of disease progression. The original Artelon CMC Spacer was launched in the U.S. in 2005. Since then, over 4,500 procedures have been performed. In 2006, the Artelon CMC Spacer LG was introduced to treat patients with larger anatomies. In 2007, the line was expanded with the Artelon CMC Spacer Arthro and the Artelon STT Spacer.

The Artelon® CMC Spacer Arthro was designed to allow minimally invasive, arthroscopic implantation in the joint between the first metacarpal and the trapezium. By avoiding violation of the joint capsule, the procedure may offer significant advantages to surgeons and their patients such as maintenance of joint stability, faster recovery and less pain.

The Artelon STT Spacer is implanted into the scapho-trapezial-trapezoidal (STT) joint at the base of the thumb. The Artelon STT Spacer is similar in size to the Artelon CMC Spacer LG, except that it has a “single wing” design (an L-shape vs. a T-shape). The spacer is designed to preserve the STT joint and to help restore joint function while minimizing the need to sacrifice healthy bone and tissue.

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The OrthADAPT™ Bioimplant is a highly organized Type 1 collagen scaffold intended to provide support for ligament and tendon repairs in a variety of surgical applications.

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The OrthADAPT™ Bioimplant is designed for a wide variety of soft tissue repairs, including orthopaedic, sports medicine, and foot and ankle applications.

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A New Orthopaedic Imaging System: EOS, Ultra Low Dose 2D/3D

Introduction
EOS, a new orthopaedic imaging system developed in Europe by the French company biospace med, has recently been cleared by FDA for sale in the U.S. The system was developed by Georges Charpak, who in 1992 won the Nobel Prize for his invention of a new high-energy physics particle detector which has been incorporated into EOS. Due to the design properties of the detector and configuration of the imager, the EOS system (shown in Exhibit 1) allows x-ray imaging to be performed at a much lower dose, with very high contrast and without the distortion inherent in longer length film or digital imaging systems.

Exhibit 1: EOS 2D/3D System

While the new imaging detector concept was based on Charpak’s technology, image quality and product design specifications were a direct result of a collaboration between Charpak and several physicians and biomedical engineering partners, most notably French orthopaedic surgeon, Dr. Jean Dubousset, and pediatric radiologist, Dr. Gabriel Kalifa.

The clinicians identified a variety of unmet orthopaedic imaging needs, such as the need to create undistorted, long length images without digital stitching. Also desired were accurate weight-bearing images that permitted 1:1 measurements along with visualization of the skeleton in a three-dimensional fashion (3D). In addition, because Dubousset is a pediatric orthopaedic surgeon and Kalifa a pediatric radiologist, both drove the design specification to reduce dose to the patient. As a result, EOS delivers an up to ten times lower dose than conventional radiography and up to 1,000 times less of a dose than CT. The elevated radiation dose to the population as a result of medical imaging is receiving recent attention in the media and is particularly critical for the pediatric population.2

EOS: 2D Imaging System
EOS digital x-ray imaging acquisition system is based on Charpak’s novel gaseous particle detector technology. The imaging gantry allows for the simultaneous acquisition of two orthogonal planar images in a vertical scanning mode. The architecture of the image acquisition method utilizes the technique of linear slot scanning (See Exhibit 2), which facilitates use of a unique 3D reconstruction algorithm, contained in a companion workstation called sterEOS.3

Exhibit 2: EOS Scanning Technique

The gantry is composed of two sets of detectors and x-ray tubes positioned orthogonally and supported by a mobile C-arm. This C-arm moves vertically, guided by three cylindrical slide bars. The patient is positioned at the intersection of the two x-ray fan-beams which scan the patient vertically. A single scan will simultaneously produce both AP and lateral images of the patient. Each imaging chain is composed of the x-ray source (tube), the beam shutter, the collimation elements and the x-ray linear detector. Fan beams are collimated both vertically to match the height of the detector entrance slit, and horizontally to limit x-ray to the width of the patient region of interest.

continued on page 32

1 Corporate headquarters for biospace med is in Paris, France and in Atlanta, Georgia, USA, with an office in Montreal, Canada. www.biospacemed.com
2 “Breast Cancer Mortality After Diagnostic Radiography” Spine Vol. 25, #16, p. 2052-2063
3 sterEOS has been designed as a 3D and orthopedic workstation and is currently under review by the FDA, and is therefore not yet approved for commercial sale in the US. sterEOS is available commercially in Canada and Europe.
K-Wire Bender/Cutter
Can bend and cut K-wires measuring 2 mm to 1.5 mm in diameter. Designed to allow bending of K-wires without causing mechanical stress while traversing bone.

Cannestra Subtrochanter Fracture Reduction Clamp
Designed to help reduce comminuted intertrochanteric and subtrochanteric fractures. In this figure, the clamp is shown at its end to avoid placement into the fracture bed.

Cutting
The K-wire is inserted into the clamping apparatus (the spring clip). The bending clip adapts to the shape of the apparatus.

Bending
The clamp is inserted into one of the sides of the apparatus. The clamp is then bent to the desired angle and the k-wire is inserted into the apparatus.

Threaded K-Wire Removal Forceps
Facilitates the removal of threaded K-wires. For 1 mm threads. Made of stainless steel.

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Used to handle tensioning wires around a bone. Can be used on wires up to 10 mm. Diameter.

K-Wire Inserter/Extractor
Features a shaped tip for better vision, helps simplify difficult techniques. Made of stainless steel.

Durkan Ratchet Bone Clamp
Design of ratcheting mechanism allows for quick tightening and releasing around the bone.

Enquiry No 10

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Vertical linear scanning allows the acquisition of long length images without being limited by the detector’s vertical dimension. Full spine images are easily created in about 12 seconds for an adult and six seconds for a child. The EOS system has a scanning range of up to 175 cm and a scanning speed of up to 30 cm/sec.

Because the frontal and lateral images are taken simultaneously in a bi-plane configuration, they are perfectly aligned and registered allowing length and angle measurements to be made from within 3D space. Since all radiographs are projections of a 3D structure onto a two-dimensional (2D) plane, and therefore contain projection related errors, sterEOS workstation provides a 3D ruler to enable length and angle measurements to be made in 3D space. (See Exhibit 3.)

Exhibit 3: EOS Digital X-ray Images

The slot scanning methodology further contributes to both image enhancement and reduced dose by rejecting all scattered radiation. This drastic reduction of scattered radiation leads to an improved signal-to-noise ratio at the entrance of the detector, which translates into image quality improvement and the capacity for significant dose reduction while maintaining the same level of clinical information.

As one example, a comparative study performed at Erasmus Hospital, Brussels and St. Vincent de Paul, Paris on 64 scoliosis patients compared radiation dose between EOS and conventional screen-film systems\footnote{Le Bras, A. Dorion, I. Feray, S. Maccia, C. Parent, S. Kalifa, G. Low Dose 2D-3D Xray scanning images for Osteo-Articular Pathologies: Initial Results on Scoliotic Children Population. Submitted for publication: European Radiology 2006.}. Based on this study of 64 patients, EOS dose measurements (Entrance Surface Dose and Entrance Surface Air Kerma) were 85 to 89% below those obtained using conventional screen-film modality. In addition, image quality scores yielded a significantly higher score for EOS than for screen-film images. A sample of the image quality comparison between radiographs provided by both EOS and screen-film for the same subject is shown in Exhibit 5: a) EOS images of a whole spine, AP view; b) corresponding screen-film image; c) EOS image of a whole spine, lateral view; d) corresponding screen-film image. Because of the lower dose and higher image quality, it was concluded that EOS would be preferable to use in place of traditional radiography systems.

Exhibit 5: EOS vs. Screen-film Image Quality Comparison

sterEOS: 3D Reconstruction

In addition to the basic 2D imaging capabilities, sterEOS is a workstation which provides the ability to obtain 3D weight-bearing...
reconstructions. Reconstruction of the 3D bone envelope is performed using both AP and Lateral views that have been acquired simultaneously, and an a-priori 3D statistical model of human spines. This model has been constructed by digitizing the 3D shape of bones over a large population of healthy and pathologic subjects and estimating the statistical relationships between the critical parameters describing the 3D shape of individual bones as well as the relationships between related bones, such as the vertebrae of the spine.

The user initiates the reconstruction process by positioning, on the AP and lateral view, a few anatomical landmarks as shown in Exhibit 6. These landmarks, with the help of edge detection algorithms and statistical inference, allow the software to produce a 3D reconstruction. This 3D reconstruction can then be manipulated by the operator to produce a 3D rendering (See Exhibit 7).

Exhibit 6: Anatomical Landmark Placement

Exhibit 7: 3D Spine Rendering

Currently, sterEOS allows the user to create a 3D rendering of the spine; a lower extremity module is currently in development. As the model is created, the system identifies the nature of each bone and critical reference points. Once the 3D model is complete, because each anatomical area or point of interest is known and located in space, the software can automatically generate over 100 angle and length calculations which have been pre-programmed into the system, including Cobb angle, Kyphosis and Lordosis, Pelvic Parameters and Vertebral Rotations. Unlike calculations made from 2D x-ray images distorted by the conical projection inherent to 2D detector usage, these calculations are accurate because they have been computed from within 3D space, which should enable more accurate and effective diagnosis, treatment and surgical planning. In addition to the calculations, the software allows the user to highlight individual structures and adjust the angle of view from which the image is seen by the operator. This enables new planes of view, such as the “bird’s eye view,” allowing the view from above, as shown in Exhibit 8.

Exhibit 8: 3D Spine Rendering: Bird’s Eye View

The combination of low dose, 3D weight-bearing images and the development of accurate 3D renderings and associated calculations gives various medical specialties access to new and more accurate information which should lead to enhanced therapy decision making, and hopefully improved patient outcomes.

Clinical Application

The imaging system is particularly well suited for pathologies such as scoliosis and adult spine, hip and knee replacements, as well as other orthopaedic issues that require a weight-bearing assessment for optimal treatment.

One of the most promising applications is using EOS and sterEOS to monitor and treat the progression of scoliosis. Because scoliosis is a 3D spinal alignment issue, the deformation cannot fully be appreciated on planar x-rays. The 3D rendering that sterEOS produces will provide physicians a more accurate and thorough understanding of a patient’s spinal deformation. For example, the following pediatric patient presented with idiopathic scoliosis and was examined using EOS by Dr. Dubousset at Saint Vincent DePaul Hospital in Paris, France. Bracing was recommended by the patient’s physician based on the mild extent of the curve. As seen in both the frontal full-spine EOS digital x-ray, Exhibit 9 of the patient in the upright position, and the frontal sterEOS 3D reconstruction of the spine, pelvis and rib cage, Exhibit 10, when the patient is wearing the brace, the spine seems rather well realigned. The derotation of the scoliotic curve seems satisfactory as well, and therefore, based on the frontal and sagittal 2D and 3D views, it would be assumed that the brace had provided the expected result in terms of correcting the scoliotic deformities.

Exhibit 9: EOS X-rays

Pediatric Patient, x-ray image without brace

Pediatric Patient, x-ray with brace
Exhibit 10: sterEOS 3D Reconstructions

On the other hand, when taking full advantage of the weight-bearing 3D reconstruction, and orienting the 3D image to a top down view, as exhibited in Exhibit 11, it is easily seen that not only does the brace not correct the deformity of the rib cage, but even worse, it increases this deformity. In this particular case, the brace was harmful to the patient because it restricted thoracic expansion and applied pressure on the wrong side of the rib cage, thus increasing rib deformity. In this example, the patient can have better brace placement and adjustment leading to improved non-surgical outcomes. Furthermore, because the majority of scoliosis patients are children who must be imaged regularly, EOS now offers a low dose option for patient follow up.

Exhibit 11: 3D Top-down Views

Another clinical application involves surgical planning for hip and knee replacement surgeries. The full length, weight-bearing imaging capabilities of EOS provide physicians with a global assessment and the relative positioning of each joint, with respect to each other. Equally important is the benefit that 3D provides in terms of accurate pre-operative measurements. For example, EOS 3D hip calculations can automatically give neck shaft angle and assess the presence of femoral rotation or torsion. This is vital to all orthopedic replacement surgeries because it allows for optimal implant selection and placement. Further, when 3D planning is performed for these surgeries, it is often done in CT which is not reflective of the weight-bearing, functional position of the hip and pelvis. Using diagnostic images made in the supine position leads to significant changes in relative position of the bones and joints to one another and ultimately changes the clinical parameters and measurements that are made for preoperative planning.

Various applications are also being pursued such as osteotomy planning and treatment options for degenerative spine and balance deterioration. Overall, EOS offers a wide variety of clinical applications for diagnosis and treatment planning, as well as the ability to replace normal x-ray follow ups with a lower dose option.

Didier Saint-Félix, Ph.D. is Chief Operating Officer, Head of R&D at biospace med. Didier has his Electrical Engineering diploma from Ecole Nationale Supérieure d’Electricité in Paris and a Ph.D. in signal processing. He has 30 years of R&D and commercialization experience in launching a variety of “first of a kind” medical imaging systems. He joined GE Healthcare in 1986 and developed the first 3D angiography system, and then led the development of GE’s digital mammography system. Didier is also a quality and regulatory affairs specialist in medical imaging and has led the 6-sigma program across global engineering teams. Dr. Saint-Félix can be reached at info@biospacemed.com.

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Enquiry No 12
Much to my chagrin, I have resigned myself to the fact that my regular contribution to this esteemed publication is becoming more of a gossip column than an erudite review of the medico-legal issues facing the orthopaedic industry. Not that I necessarily mind being “in the know” on such issues, but it does make a statement both about the industry in general and what is making news in it specifically. That said, we cannot avoid the fact that one goal the government had in mind when it began its investigations into the orthopaedic device industry has been achieved; we are all, attorneys, doctors and manufacturers alike, talking about little else these days besides the heightened scrutiny in our little part of the world and what it will mean as we move forward. And we appear to be making news well beyond the boundaries of our trade magazines and journal clubs. Talk abounds of physicians receiving subpoenas and company investigations digging deeper and deeper into the sales and marketing practices of all manufacturers, big and small. Devices and the doctors who implant them have been featured so far this year in The Wall Street Journal, The New York Times, and various regional papers throughout the country (most notably and predictably Newark’s hometown paper, The Newark Star Register). Congress has more than three different committees cogitating on various issues touching on device industry including disclosure of financial relationships to patients and, dare I say it out loud, the appropriateness of these relationships and that his intention is not to eradicate them altogether. Perhaps most disturbing to me is a recent article that came across the Dow Jones Newswires indicating the very real possibility (and rumor on the street has it, a probability) that Zimmer, the largest of the device manufacturers operating under a Deferred Prosecution Agreement, will “buy out” all of its surgeon contracts. Presumably this colossal task is being undertaken to start over with these relationships in a more compliant way, which is a good thing, but the possibility remains that this may signal the beginning of the end for surgeon/industry collaboration. What if Zimmer determines that it does not want to move forward with any contracts with physicians? Will industry ever look the same again? Will we ever be the same again?

U.S. Attorney Christopher Christie insists that he recognizes the value of these relationships and that his intention is not to eradicate them altogether. I believe him. But I am very afraid that an unintended consequence of all of this emphasis on compliance to a level of minutia not seen before will result in just that, an abrupt halt to the very valuable work in which physicians engage every day around the country to develop new and improve existing technologies.

I have been a staunch proponent of change in this industry. I have seen some of the abuses that Mr. Christie alleges run rampant, and, like every one of you, I know at least one doctor who has alluded to the fact that he thinks it is perfectly appropriate for his loyalty to a particular manufacturer to be compensated with cash. (No, I will not identify this individual if asked, and yes, he is the very rare exception to the rule.) I also believe that curtailing excessive spending on dinners, travel and gifts makes perfect sense. We have frowned upon such indulgence in corporate America, why not medical America? But that is where my enthusiasm for change ends because I see the pendulum swinging dangerously far in the opposite direction. I will never counsel a physician client to skirt the rules or assume that they do not apply to him or her because he or she doesn’t like them. But I will say that I feel their pain. The level of regulation with which they are being faced in every aspect of their lives is unprecedented. And the idea that I can take a surgeon client to a ball game, but a sales representative cannot, makes little sense to me. I realize that it is a slippery slope and that being vigilant about such matters is critical. But I also know that isolating physicians and wholly eradicating their relationships with industry, corporate personnel and sales representatives alike, is decidedly not good for patient safety or the advancement of medicine as a whole.

I have expressed my dissatisfaction about this in previous articles, but feel compelled to do it again. I will likely need a new hip or knee before my time in this incarnation is over, and while the existing options are good, even great in some respects, if I can hold off for thirty more years the way my mom did, the sky is the limit. With continued research and development, my knee could be made of a material so light I would not even know it was there. And perhaps this new magic material will be so durable that I will live to be one hundred! And maybe it will have such good flexion and rotation that I will be able to continue all of the sporting activities that I love and perhaps add a few more! I have no idea what the chances of achieving these or other major advancements in orthopaedic medicine are with the way such research and development is conducted. What I do know for sure is that if you take physicians out of the mix and rely solely on the, albeit talented, but non-medical engineers and other personnel who assist with bringing new ideas to the market, I will never get my magic knee…and neither will anyone else.

The Law Offices of Teresa Ford, PC (www.tfordlaw.com), located in Houston, Texas, specialize in healthcare and medical device issues. Areas of expertise include healthcare compliance program structuring and training, as well as advising individual physician clients. Founding partner Teresa Ford spent many years in the medical-legal arena, most recently as senior counsel for Saltzer Medica USA Inc. She can be reached at 832-251-9595 or tford@tfordlaw.com.

Enquiry No 43

*For example, some manufacturer booths at AAOS actually posted notices declaring that snacks and beverages would not be provided this year in compliance with AdvaMed and other industry guidelines and regulations! Can this really be what the government was trying to accomplish?*

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¹ Data on file at Biomet Sports Medicine, Inc. Bench test results are not necessarily indicative of clinical performance.

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**3DM External Fixation Products**

The 3DM-SO Cannulated Drill Pins with Angle Blocks allow for concentric placement of drill-pins (self-drilling and self-tapping) over a guide wire and eliminate dull/wandering drill bits. The angle blocks facilitate oblique placement on external fixation rings and rods, allowing for better pin spread, lighter frames and stronger constructs. For further details, contact Beverly Laird, Ph.D. at bev@3dmedicalconcepts.com.

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**rHead Plating System**

Small Bone Innovations, Inc. (SBI) has introduced its rHead™ Plating System for internal fixation of proximal radius fractures. The comprehensive rHead Plating system offers four different plates with various rim and neck designs for increased reconstructive options, plus locking and non-locking screws.

The rHead plates feature a low profile for smooth annular ligament translation during pronation and supination. A unique tripod locking screw helps provide a stable buttress support configuration. rHead plates are highly contoured with an anatomic design to minimize bending. The system offers traditional non-locking, low profile side screws to capture fragments and a locking screw option in the shaft of the plate.

The rHead Plating System is part of SBI’s EMS (Elbow Management System), the most complete system available to manage the treatment algorithm.

The SBI rHead Plating System has received 510(k) clearance from FDA.

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MEDARTIS®, headquartered in Basel, Switzerland, is an innovator in the use of polyaxial locking plate and screw fixation for the treatment of fractures of the hand and distal radius. The APTUS® product line features anatomically-designed hand and radius fracture plates.

The APTUS® Hand system offers low profile locking and non-locking plates with a variety of screw diameters to manage all types of fractures. The APTUS® Radius system provides various geometries to address acute fractures, as well as corrective osteotomies.

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**Phoenix™ Tibial Nail**

Biomet Trauma has introduced the Phoenix™ Tibial Nail featuring state of the art locking, compression and optimized screw positions with next generation instrumentation. Biomet Trauma’s innovative CoreLock™ technology provides a patent pending, pre-assembled setscrew that dually locks the proximal oblique screws designed for enhanced stable fixation of proximal tibial fractures and offers up to 5mm of inboard compression for acute fracture reduction. In addition, the nail features a distal bone screw cluster that maximizes the working length of the nail enabling surgeons to treat from the most proximal to the most distal tibial fractures. Exclusive to the Phoenix Tibial Nailing System is a 7.5mm cannulated tibial nail that is reportedly the smallest in the industry. The Phoenix Tibial Nail also offers surgeons a full complement of innovative and user-friendly features that will enable them to keep pace with the growing demand for such procedures.

Biomet Trauma
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www.biomettrauma.com
Enquiry No 49
Biologic Joint Replacement or Why Airplanes Fly

When everything seems to be going against you, remember that the airplane takes off against the wind, not with it.
—Henry Ford

Some look at things that are, and ask why. I dream of things that never were and ask why not?
—George Bernard Shaw

Total joint replacement and specifically knee and hip arthroplasty is undoubtedly one of the most successful operations ever devised. Medicare data evaluating the improvement in quality of life/years versus the number of dollars spent per procedure has shown that no other operation aside from cardiac bypass comes close to total joint replacement outcomes.

The world changed for hip surgeons when John Charnley published “Arthroplasty of the Hip: A New Operation” in 1961. However, with this great leap in surgical technology came an entirely new set of problems with which orthopaedic surgeons, engineers and biologists have continued to struggle for over forty years.

Beginning in the late 1800s, most procedures for hip arthritis were femoral replacements. Glass, vulcanized rubber, ivory and metal articulations were all tried with limited success, but all eventually succumbed to early failure. With the advent of total hip arthroplasty, many of the problems associated with the earlier procedures were eliminated and the procedure rapidly gained wide acceptance. However, with the tremendous growth in the number of replacements being performed came an expansion of the indications for the procedure to younger and more active patients. With the use of joint replacements in younger individuals came increased expectations from patients for higher levels of activities post-implantation. Higher loads and stresses experienced by the implants used in these patients ultimately lead to higher wear and loosening rates.

The focus then turned to improving surgical techniques and developing materials with lower wear rates and increased toughness, strength and durability.

In his original article, Charnley stated, “Neither surgeons nor engineers will ever make an artificial hip joint which will last 30 years and at some time in this period enable the patient to play football.” To this day nearly 50 years later this prediction holds true, as the early failure of Bo Jackson’s hip replacement showed all too well.

The aforementioned basic tenet remains true today for the simple reason that total hip replacement remains essentially the same operation as it was in 1961. While vast improvements in wear rates have been achieved with highly cross-linked polyethylene, ceramic and metal articulations, implant design and modularity and improvements in surgical techniques, the successor to Charnley’s original operation has yet to be devised. This is so because present day joint replacement surgery is not really a joint replacement at all but rather a joint substitution—a metal substitution for the native bone and cartilage construct.

The concept of being able to replace damaged bone and cartilage in an arthritic joint with living bone and cartilage has long been considered the “holy grail” of joint replacement surgeons, but unfortunately little progress has been made in this area. Certainly the entire field of tissue engineering has only recently gained in its maturity and has yielded innovative approaches to address bone and tendon defects identified clinically and in the operating room. Cartilage, on the other hand, has proven far more difficult to engineer into clinically useful material. While clinical trials are underway for several cartilage repair techniques, other than the Genzyme procedure no cartilage constructs are commercially available for surgical implantation—let alone entire bone and cartilage articulations.

For many technical reasons, repairs of even isolated cartilage defects have been difficult to achieve and other than occasional case reports outside the U.S. for small joints, no earnest attempt has been made at engineering an entire biologic joint replacement. Furthermore, if one takes into consideration the forces generated across large joints in humans, it is difficult to imagine how any newly-constructed bone and cartilage articulation would be able to survive in vivo without dissociating or collapsing.

Our collaboration with Dr. Jeremy Mao of Columbia University has recognized this seeming dilemma and we have proposed a different strategy to satisfy the need for early weight bearing strength while at the same time providing the proper environment for a cell-based construct to mature into a functional biologic joint replacement.

Rather than attempt to engineer a matrix of bone and cartilage which is sufficiently strong to survive the forces seen across a human hip joint at the time of implantation, we have taken the approach that this probably cannot be done with an isolated tissue-engineered construct at the present level of understanding in the field. Instead, we have designed a multi-phase delivery system that serves as a temporary supporting structure for a stem cell osteochondral construct that grows in situ after implantation. After the construct matures to the point of loading bearing capacity, the delivery system, which is initially load bearing, gradually becomes load sharing and then ultimately is resorbed in a step-wise predetermined manner. While the consensus is that with what is known at the present this cannot be achieved, recent data generated in Dr. Mao’s

continued on page 43

Author: James M. Weiss, M.D.
laboratory has given us evidence that this may be technically feasible. I am reminded of a story told to me by the former director of the USPTO concerning the early days of the patent office. From the time that the patent office was founded by Thomas Jefferson in 1790 up until 1900, miniature working models had to be submitted for review before a device could be considered for a patent. As technology evolved the need for change was recognized, and in 1900 a blue ribbon panel of members of the National Academy of Sciences as well as academics was assembled to enact a new set of rules. The result was that a written document would be deemed acceptable for all patent submissions with two exceptions. There were two phenomena which were considered to violate the laws of physics and so for these two instances, a continuous motion machine and a heavier than air flying machine, a working model would still be required. Following the events of December 17, 1903, the panel was forced to reconvene and drop one of their exceptions.

It is difficult to say what is impossible, for the dreams of yesterday are the hopes of today, and the realities of tomorrow. —Robert H. Goddard

Why do planes fly? Because two bicycle repair shop workers from Dayton, Ohio were not invited to that 1900 meeting and through impossible odds had the vision and the determination to make it happen.

James M. Weiss, M.D. is an orthopaedic surgeon in private practice in Chevy Chase, Maryland. He is also the Chief Executive Officer of Joint Analogy Technologies Inc. He can be reached at jweissmd@verizon.net or 301-540-4791.
Testimony of Gregory E. Demske, Assistant Inspector General for Legal Affairs

Senate Special Committee on Aging Hearing: February 27, 2008

On February 27, 2008, the U.S. Senate Aging Committee held a hearing entitled “Surgeons for Sale? Conflicts and Consulting Payments in the Medical Device Industry,” in order to “examine the relationships between medical device manufacturing companies and surgeons.” Among those who testified were representatives from large and small device companies, AdvaMed, and other relevant parties. The testimony from the Office of Inspector General set the tone for the discussions. It is printed here in its entirety.

Those wishing to read the testimony of others can find them at aging.senate.gov/hearing_detail.cfm?id=293677&0.

Good morning, Mr. Chairman and members of the committee. I am Gregory Demske, Assistant Inspector General for Legal Affairs in the Office of Inspector General of the Department of Health and Human Services. I appreciate the opportunity to appear before you today to discuss the financial relationships that exist between physicians and the medical device industry. These financial relationships can benefit patients and Federal health care programs by promoting innovation and improving patient care. However, these relationships also can create conflicts of interest that must be effectively managed to safeguard patients and ensure the integrity of the health care system.

In my testimony, I will discuss the risks associated with industry-physician financial relationships; highlight some of our recent investigations that illustrate these risks; and describe ways to mitigate these risks through enforcement actions, outreach to promote compliance, and increased transparency.

Relationships Between the Medical Device Industry and Physicians

Relationships between physicians and the health care industry, including pharmaceutical and device manufacturers and suppliers, can advance medical science and benefit patients. In the development of new technologies and products, the interaction between device manufacturers and health care professionals can be especially valuable because physicians play an essential role in the development, testing, and extensive training involved in producing effective and safe medical devices, such as heart valves, pacemakers and medical lasers. Physicians also provide ideas and feedback, conduct research and clinical trials, and share their knowledge through participation in medical education programs. Device companies can legitimately compensate physicians for their actual time and intellectual contributions to product innovations and training in the appropriate use of devices.

However, in an environment where physicians routinely receive substantial compensation from medical device companies through stock options, royalty agreements, consulting agreements, research grants, and fellowships, evidence suggests that there is a significant risk that such payments will improperly influence medical decision making. Researchers reporting in medical journals, such as the Journal of the American Medical Association and the New England Journal of Medicine, have found that such financial industry-physician relationships are pervasive and that the impulse to reciprocate for even small gifts has a powerful influence on behavior. Although most physicians believe that free lunches, subsidized trips, or gifts have no effect on their medical judgment, there research has shown that these types of perquisites can affect, often unconsciously, how humans act. For example, physicians who request additions to hospital drug formularies are far more likely than their peers to have accepted free meals or travel funds from drug manufacturers. Similarly, a device company’s largess may influence a physician to favor the company’s products. As the American Academy of Orthopaedic Surgeons observed, “[w]hen an orthopaedic surgeon receives anything of significant value from industry, a potential conflict exists which should be disclosed to the patient.”

Physicians play a critical role in deciding which medical devices are used in the treatment of their patients. Complex medical devices are generally implanted or otherwise used in a hospital procedure or inpatient stay for which the hospital is reimbursed. The treating physician generally decides or strongly influences the decision regarding which medical device should be used in this hospital setting. Therefore, a device manufacturer has a strong financial incentive to persuade treating physicians to use or recommend the manufacturer’s devices.

We do not know how much money device manufacturers pay to physicians. However, the Government’s recent investigations of several manufacturers of hip and knee surgical implants offer some insight. In 2005, the orthopedic device market for hips and knees witnessed domestic sales in excess of $5.1 billion and worldwide sales of more than $9.4 billion. We found that during the years 2002 through 2006, four manufacturers (which controlled almost 75 percent of the hip and knee replacement market) paid physician consultants over $800 million under the terms of roughly 6,500 consulting agreements. Although many of these payments were for legitimate services, others were not. The Government has found that sometimes industry payments to physicians are not related to the actual contributions of the physicians, but instead are kickbacks designed to influence the physicians’ medical decision making. These abusive practices are sometimes disguised as consulting
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contracts, royalty agreements, or gifts. The companies and physicians who engage in such kickback schemes are subject to criminal, civil, and administrative sanctions.

Additionally, physician ownership of medical device manufacturers and related businesses appears to be a growing trend in the medical device sector. These business ventures raise substantial concerns that a physician’s return on investment from the venture may influence the physician’s choice of device. In some cases, physicians could receive substantial returns while contributing little to the venture beyond the ability to generate business for the venture. As we cautioned in a widely-disseminated letter to a medical device trade association, “[g]iven the strong potential for improper inducements between and among the physician investors, the entities, device vendors, and device purchasers, we believe these ventures should be closely scrutinized under the fraud and abuse laws.”

The financial relationships between device manufacturers and physicians merit scrutiny under anti-fraud statutes because the relationships raise the types of risks that those statutes are designed to address. The consequences of industry-induced bias include risks to patients, health care programs, and scientific research. When a physician’s self-interest compromises independent judgment, the patient faces the risk that the physician is making decisions that are not in the patient’s best interest. Additionally, excessive payments to physicians increase health care costs and may result in unfair competition. When a device manufacturer pays a physician to influence the physician’s use or recommendation of its products, rather than to advance a legitimate medical interest, the additional costs are passed on to the patients, Federal health care programs, and private insurers. Such payments can also distort the market place by providing an unfair competitive edge to the company making the payments, regardless of the relative therapeutic value of the company’s products. Finally, corrupt payments can compromise medical research independence and the standards of scientific integrity.

Relevant Federal Anti-Fraud Statutes

Several Federal statutes are relevant to manufacturer-physician payment relationships. The False Claims Act is the Federal Government’s primary civil enforcement tool for addressing fraud. Under the False Claims Act, the Government may obtain substantial penalties against any person who knowingly submits, or causes the submission of, false or fraudulent claims to the Federal Government. (See 31 U.S.C. §§ 3729–3733.) The False Claims Act allows the filing of qui tam lawsuits against individuals or companies that have defrauded the Federal Government. Many people who file qui tam lawsuits (called relators) are employees or former employees of companies that committed the fraud.

The Federal anti-kickback statute makes it a criminal offense to knowingly and willfully offer or pay remuneration to induce the referral of Federal health care program business. The statute also criminalizes the knowing and willful solicitation or receipt of remuneration in exchange for such referrals. (See 42 U.S.C. § 1320a–7b(b).) The prohibition applies regardless of the nature or form of the arrangement. If one purpose of an arrangement is to induce referrals of Federal health care program business, the statute is violated. Whether a particular arrangement runs afoul of the statute depends on the specific facts and circumstances of the arrangement, including the intent of the parties.

The anti-kickback statute and regulations contain certain “safe harbors,” which describe arrangements that do not violate the statute if every condition of the particular safe harbor is satisfied. OIG’s regulatory authority extends to promulgating safe harbor regulations describing categorical practices that are permissible. Compliance with safe harbor is

volatile, however, and arrangements that do not fit in a safe harbor are not necessarily illegal. Rather, they must be evaluated under the statute on a case-by-case basis.

OIG administrative authorities complement criminal and civil enforcement by providing an additional avenue for sanctioning persons who have defrauded Federal health care programs. For instance, OIG has the authority to exclude individuals and entities from participation in the Federal health care programs for engaging in a range of abusive practices, including false claims and kickbacks. (See 42 U.S.C. § 1320a-7.)

OIG may also pursue violations of the anti-kickback statute under a provision of the Civil Monetary Penalties Law. (See 42 U.S.C. § 1320a-7a (a)(7).) Civil Monetary Penalty (CMP) cases can be attractive alternatives to criminal and civil enforcement for several reasons. For example, relative to the False Claims Act, the CMP provides a more direct vehicle to address parties to a kickback scheme regardless of whether anyone actually submits claims. This makes the kickback CMP particularly relevant in cases in which a device manufacturer is paying a physician to induce the physician to recommend the manufacturer’s device for use in a hospital procedure. In such a case, the claim is submitted by the hospital, which is not a party to the financial arrangement. CMP remedies in kickback cases include monetary penalties of up to $50,000 for each act (offer, payment, solicitation, or receipt of remuneration), assessments of up to three times the amount of remuneration, and exclusion from participation in Federal health care programs.

Recent Enforcement Actions

OIG, together with its Government partners, plays a substantial role in enforcing the fraud and abuse laws through criminal, civil, and administrative actions. In recent years, OIG and the Department of Justice (DOJ) have investigated cases involving industry-physician financial relationships in both the pharmaceutical and medical device areas. In these cases, we have seen medical device manufacturers offering physicians lucrative consulting agreements to acquire new business and to maintain physician loyalty. We have also seen instances in which the physicians, in turn, have signaled to the industry that their loyalties and business are for sale to the highest bidder. In some cases, it comes down to how much each company is willing to pay for a physician’s business, which is often being simultaneously solicited by multiple competing companies.

Kickbacks offered to physicians by medical device manufacturers take a variety of forms, ranging from free practice management services to all-expense-paid trips and sham consulting agreements. To illustrate these arrangements, I will summarize several settlements with device companies and a recent conviction of a physician.


In September 2007, four major medical device manufacturers entered into civil settlement agreements with the Government collectively totaling $311 million to resolve allegations under the False Claims Act. The Government alleged that the four companies provided financial incentives in the form of consulting agreements, lavish trips, and other perks to induce physicians to use a particular company’s artificial hip and knee reconstruction and replacement products.

The investigation found that, although many payments were provided for legitimate services, in certain consulting arrangements the companies derived little value beyond the acquisition of increased sales of artificial hip and knee implants used by the consulting surgeons. The companies

continued from page 44
also failed to oversee and audit the work performed by the surgeons under the consulting agreements. For example, the surgeons engaged in “work” activities that involved minimal time, sometimes for as few as 10 minutes. Although the remainder of the day was available for recreational activities paid for by the company, the consultants were compensated $5,000 for a full day of work.

• Consultants billed for training sessions that involved sales representatives observing the surgeon while in the operating room. Some of these training sessions were held for experienced sales representatives who, as part of their jobs, had been servicing the surgeons in their sales regions for some time. These sales representatives were already required to be present in the operating room with the surgeons to assist them with the procedures. These training sessions lasted for 1 to 2 hours, but the consultants billed for an 8- to 10-hour workday.

• Some companies entered into product development agreements with consultant physicians, offering them royalty payments once the products were launched. These agreements provided for annual payments of hundreds of thousands or millions of dollars for up to 20 years. The design teams included up to 20 physicians, some of whom were added after the projects were more than halfway completed. The companies often did not measure the contributions of individual physicians and up to half the members of some teams appeared to have performed little or no work.

The Government alleged that by offering illegal inducements, the companies violated the False Claims Act by causing hospitals to seek and obtain reimbursement from Medicare. As a part of the global resolution, the companies agreed to subject the services that they provided to the company to support the consulting fees. Some consulting agreements had only vague requirements for these reports. When the consulting agreements did include specific requirements, these reports often failed to include the required information or were drafted by sales representatives rather than by the consultants.

In addition to reports documenting services provided, some companies paid consultants a fee, typically $5,000, for each quarterly report that included information on market trends, activity in the operating room, and product issues. However, these work reports typically included only cursory descriptions and were often duplicated from quarter to quarter. Many of these quarterly reports were of little or no value to the companies.

• The companies sponsored consultant panel meeting at resort locations and reimbursed the physicians for travel expenses. These meetings would only be held for a few hours each day and physician consultants who presented at these meetings typically spoke for individual physician panels, sometimes for as few as 10 minutes. Although the remainder of the day was available for recreational activities paid for by the company, the consultants were compensated $5,000 for a full day of work.

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The Government alleged that by offering illegal inducements, the companies violated the False Claims Act by causing hospitals to seek and obtain reimbursement from Medicare. As a part of the global resolution, the four companies agreed to certain prospective reme-
Continued from page 47

fake research studies. The investigation found that Dr. Chan stopped using one company’s products after it refused to pay him kickbacks. Soon thereafter, Dr. Chan signed a $25,000 consulting agreement with Blackstone and switched to using its products.

Mitigating the Risks Inherent in Physician-Industry Financial Relationships
As I have mentioned, physician-industry interactions can provide tangible benefits to patients and the advancement of medical science. These interactions can also create conflicts of interest that, if not managed effectively, can pose significant challenges to medical professionalism and undermine the integrity of the Nation’s health care system. Criminal, civil, and administrative enforcement is an important facet of an overall strategy to discourage financial arrangements that distort physicians’ professional judgment. However, it would be both inappropriate and impractical to rely solely on Government enforcement to address an issue of this complexity. The health care industry, medical community, and the Government must develop and implement additional approaches to reduce the risks raised by these arrangements.

For this reason, OIG commits substantial resources to encourage the health care industry to adopt voluntary anti-fraud and compliance measures. OIG promotes these efforts by providing a range of comprehensive guidance, including advisory opinions, compliance program guidance, and special fraud alerts and bulletins. All of these resources are publicly available on OIG’s Web site at www.oig.hhs.gov. OIG also engages in extensive industry outreach efforts, including providing guidance to major trade associations, legal, and compliance conferences.

As reflected in the Government’s recent enforcement actions involving the medical device industry, the anti-kickback statute plays a central role in addressing excesses in physician-industry relationships. Because the anti-kickback statute is a criminal, intent-based statute that requires a case-by-case analysis to determine whether the law has been violated, OIG’s ability to issue general guidance about the statute is limited. The safe harbor regulations issued by OIG immunize certain conduct from prosecution and provide guidance on relevant risk factors. In addition, OIG offers an advisory opinion program under which parties can obtain OIG’s legal opinion about the application of the anti-kickback statute and other OIG fraud and abuse authorities to their existing or proposed business arrangements.

Further assistance is available from OIG in the form of compliance program guidance for various health care sectors. OIG’s Compliance Program Guidance for Pharmaceutical Manufacturers (CPG) (68 FR

DOJ UPDATE

In conclusion, financial relationships between the medical device industry and physicians are pervasive and can create both benefits and risks to patients and health care programs. Effectively managing the risks associated with these financial relationships is a challenge that warrants a comprehensive strategy by Government, the health care industry, and physicians.

OIG will continue to work with DOJ and other partners to investigate and pursue cases against device manufacturers and physicians who violate fraud and abuse laws. At the same time, we will continue our outreach to the medical device industry and physicians to increase awareness of the compliance risks and the resources available to assist them in managing those risks. OIG is also considering ways to promote increased transparency of financial relationships. Efforts by Congress, industry, physicians, and academia to promote awareness of the risks of conflicts of interest, increase the transparency of these financial relationships, and implement appropriate policies to manage these risks would go a long way to safeguard patients and health care programs.

That concludes my statement. Thank you for the opportunity to testify today. I would be pleased to answer any questions that you may have.

Enquiry No 51

Consensus®
Knee System

The Normal-Knee Implant
That is Above the Norm

Enquiry No 17

Hayes Medical
(916) 335-7100
www.hayesmed.com
In 2007, the U.S. market for bone graft materials (excluding structural allograft) neared $1.9 billion. Included in this estimate are non-structural allograft, demineralized bone matrix (DBM), bone morphogenetic proteins (BMPs) and synthetics like hydroxylapatite (HA), calcium sulfate and tricalcium phosphates (TCP). By our estimates, bone graft materials were used in more than 1.4 million procedures related to revision arthroplasty, spinal and other fusions, fracture repair, repair of malunion/nonunion and other defect filling applications.

Because they have application in a variety of orthopaedic subspecialties, bone graft materials have become part and parcel of the product portfolios of more than 50 companies with FDA clearance, from biotech-oriented to broad-based orthopaedic and spine-focused entities. A number of companies from Europe and the Far East also claim FDA clearance, although many have not yet moved into the U.S. market.

While not exhaustive, Exhibits 1 and 2 provide a list of many of the bone graft materials available in the U.S. Clearly, today's orthopaedic surgeon has more than his share of biological solutions to his patient's bone void problems.

Exhibit 1: Bone Graft Materials Available in the U.S.: Synthetics and BMPs

<table>
<thead>
<tr>
<th>Company/Website</th>
<th>Product and &quot;Partnerships&quot;</th>
<th>Available Configurations/Composition</th>
<th>Regulatory Status</th>
<th>Key Differentiation</th>
<th>References</th>
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<tbody>
<tr>
<td>Acumed</td>
<td>Callos Inject and Callos Impact; Manufactured by Skeletal Kinetics; distributed by Acumed.</td>
<td>Injectable through syringe; impartable by hand / After mixing the powder and liquid components of the product, it will turn into a low crystalline HA, which is similar to the mineral phase of human bone.</td>
<td>Indicated to be injected into bony voids or gaps in the skeletal system, i.e. extremities, spine, and pelvis. (BVF) These defects may be surgically created osseous defects or osseous defects from traumatic injury to bone.</td>
<td>Increased tensile strength, increased flexural strength and increased fracture toughness (first cement to be drilled and screwed). Easy to mix and deliver. Sets in a wet environment and quickly in 5 minutes at 37°C. Cellular remodeling allows cement not to leave any gaps or voids as new bone forms in and around the implanted area in vivo.</td>
<td>1) Yetkinler DN et al. In Vitro and In Vivo Evaluation of Two Calcium Phosphate Cements. Orthopaedic Research Society Transactions Vol. 29, San Francisco, California 2004. 2) Lin J et al. Increased Fracture Toughness Improves Clinical Utility of a Novel Calcium Phosphate Cement. Orthopaedic Research Society Transactions Vol 31, 2006.</td>
</tr>
<tr>
<td>Angstrom</td>
<td>NanOss; Acquired by Pioneer Surgical. Pellets / Calcium phosphate</td>
<td>(BVF) (extremities, spine and pelvis)</td>
<td>First material that duplicates the microstructure, composition and performance of human bone. Proprietary nanocrystalline technology being developed into structural, weight bearing medical devices and injectable, endothermic, weight bearing bone cements.</td>
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<tr>
<td>Company/Website</td>
<td>Product and “Partnerships”</td>
<td>Available Configurations/Composition</td>
<td>Regulatory Status</td>
<td>Key Differentiation</td>
<td>References</td>
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<tr>
<td>A-Spine</td>
<td>Osteo-G</td>
<td>Pellets, kit (for producing paste) / Calcium sulfate dihydrate</td>
<td>BVF (extremities, spine and pelvis)</td>
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<tr>
<td>Berkeley Advanced Biomaterials</td>
<td>Bi-Ostetic</td>
<td>Granules, blocks, cylinders / 60% HA, 40% TCP</td>
<td>BVF</td>
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<tr>
<td>Berkeley Advanced Biomaterials</td>
<td>Bi-Ostetic Foam</td>
<td>Strips, sheets / 60% HA, 40% TCP + highly purified fibrillar Type I bovine collagen</td>
<td>BVF</td>
<td></td>
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<tr>
<td>Berkeley Advanced Biomaterials</td>
<td>Cem-Ostetic</td>
<td>Putty, injection kit, granules, blocks, cylinders / Calcium-based bio-compatible calcium salts</td>
<td>BVF</td>
<td></td>
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<tr>
<td>Berkeley Advanced Biomaterials</td>
<td>Geno</td>
<td>Granules / β-TCP</td>
<td>BVF</td>
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<tr>
<td>Biocomposites</td>
<td>Genex</td>
<td>Setting paste (putty soon to be available) / β-TCP, synthetic high purity CaSO₄</td>
<td>BVF (long bones, extremities, spine and pelvis); putty awaiting clearance</td>
<td>ZPC Negative Surface charge promotes cellular cascade of protein and cell attachment; patented composition stimulates dedocondral ossification via cartilage. 1) Hunt JA and Cooper JJ. The Significance of Zeta Potential in Osteogenesis. Poster presentation, Society for Biomaterials 2006 Annual Meeting, April 2006. 2) Karladani AH. Limitations of Autograft and Allograft. New Synthetic Solutions. Presented at the Iranian Medical Society Meeting, March 17, 2007.</td>
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<tr>
<td>Company/Website</td>
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<tr>
<td>Biomatlante</td>
<td></td>
<td>Granules, blocks, gel 60% HA,80% 8-TCP</td>
<td>BVF (extremities, spine and pelvis)</td>
<td>Developed biphasic ceramics 20 years ago. Macroporous structure allows for control of resorption and porous substitution; microporosity allows the diffusion of biological fluids. Saturation of ions leads to crystalline precipitation with apatite crystals, identical to those of the natural bone.</td>
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<td></td>
<td>Granules, sticks, blocks / 20% HA / 80% B-TCP</td>
<td>BVF (extremities, spine and pelvis)</td>
<td>Provides an architecture with interconnected porosity, allowing for rapid hydration with biologically beneficial fluids and immediate cell infiltration, while creating a stable osteoconductive platform of suspended B-TCP (uncalcined) in a polymer lattice.</td>
<td></td>
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<tr>
<td>Biomet</td>
<td>OsseoFit Porous Tissue Matrix; Manufactured by Kensey Nash.</td>
<td>Cylinders 15mm length x 4, 8, 10, 12 and 15mm diameters; pre-loaded in color-coded delivery device; can be trimmed to length / 80% B-TCP / (tricalcium phosphate) suspended within a Polyactic Acid (PLA) lattice and collagen composed of Type I bovine collagen.</td>
<td>BVF (extremities and pelvis)</td>
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<tr>
<td>BoneSupport</td>
<td></td>
<td>Powder in closed mixing device for mixing to paste for injection or molding / 60% calcium hemihydrate and 40% hydroxyapatite.</td>
<td>BVF (extremities, spine, and pelvis)</td>
<td>Biodegrable, injectability and penetrability and controlled bone in-growth.</td>
<td></td>
</tr>
<tr>
<td>Calcitec</td>
<td>Osteofix</td>
<td>Powder + ilastin / Calcium phosphate, sodium phosphate, deionized water and calcium oxide.</td>
<td>BVF</td>
<td></td>
<td></td>
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<tr>
<td>Curasan</td>
<td>Cerasorb</td>
<td>Granules / B-TCP</td>
<td>BVF (extremities, spine, and pelvis)</td>
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<tr>
<td>DePuy Spine</td>
<td>HEALOS Bone Graft Replacement</td>
<td>Variety of strip sizes ranging from 2.5cc to Tissue / 80% HA / 70% Type I Bone Graft</td>
<td>BVF</td>
<td>Designed to mimic appearance of immature bone (70% collagen, 30% mineral) so quickly remodels into new bone (claims that other synthetic matrices mimic the appearance of mature bone (30% collagen, 70% mineral) requiring osteoelastic activity to break down the matrix before it can be remodeled into new bone.) Peer-reviewed and published human clinical data showing equivalence to autograft. Radio-lucent (no residual calcium on post-op films as with other matrices)</td>
<td></td>
</tr>
<tr>
<td>DePuy Spine</td>
<td></td>
<td>Conduit; Distributed by both DePuy Orthopedics and DePuy Spine</td>
<td>BVF</td>
<td>Porosity. The granules have 70% porosity vs. the higher percentage in competitive TCPs. This makes the product more structurally sound and hard to crush.</td>
<td></td>
</tr>
<tr>
<td>Etx Corporation</td>
<td>Alpha-bsm</td>
<td>Powder + sterile saline - forms paste-like consistency at room temperature; can be either injected or molded and packed into the defect; hardens and sets within 20 minutes of implantation / Proprietary pure synthetic self-setting nano-crystalline calcium phosphate formulation</td>
<td>BVF (extremities, spine, and pelvis)</td>
<td>Studied in a prospective, randomized trial vs. iliac crest bone graft in tibial plateau defects. Provides synthetic material with a long working time (up to 60 minutes) and flexibility of either injecting or molding and packing into the defect. Sets isothermally, with no heat release that can affect surrounding tissue, in a wet environment. Contains proprietary microporous structure which mimics the mineral content of human bone ensuring predictable remodeling in conjunction with bony ingrowth.</td>
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</tr>
<tr>
<td>Etx Corporation</td>
<td>Beta-bsm</td>
<td>Powder + sterile saline - forms paste-like consistency at room temperature; can be self-harden and set within the defect; hardens and sets within 3-5 minutes of implantation / Proprietary pure synthetic self-setting nano-crystalline calcium phosphate formulation</td>
<td>BVF (extremities, spine, and pelvis)</td>
<td>Formulated with the same chemistry as Alpha-bsm but will eject through a 16 gauge needle and self-harden in a wet environment (with 30 MPa of compressive strength). In addition, the syringe to syringe mixing system allows for simple mixing and delivery. Same as for Alpha-bsm.</td>
<td></td>
</tr>
<tr>
<td>Etx Corporation</td>
<td>Gamma-bsm</td>
<td>Powder + sterile saline - forms a paste-like consistency at room temperature; can be molded and packed into the defect; hardens and sets within 3-5 minutes of implantation / Proprietary pure synthetic self-setting nano-crystalline calcium phosphate formulation</td>
<td>BVF (extremities, spine, and pelvis)</td>
<td>Formulated with the same chemistry as Alpha-bsm but provides a synthetic material that is simple to mix, has unique moldability and sets hard in a wet environment (with 45 MPa of compressive strength). Same as for Alpha-bsm.</td>
<td></td>
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Exhibit 1, continued from page 51

52 Orthopaedic Product News • May/June 2008

Exhibit 1, continued on page 54
Fill the void.

OsseoFit™ Porous Tissue Matrix™ device, developed and manufactured by Kensey Nash Corporation, is a unique resorbable bone void filler composed of an interconnected, highly porous, osteoconductive scaffold.

Features
- Intended to be gently packed into bony voids or gaps of the extremities or pelvis caused by trauma or surgery that are not intrinsic to the stability of the bony structure.
- Resorbable biomaterial is designed to be completely replaced by bone during the healing process.
- Unique architecture facilitates cell infiltration and bone maturation.
- ~3% swelling after hydration provides for solid anchorage.
- Can be hydrated with sterile fluids such as autogenous blood products (bone marrow aspirate, platelets and blood) or saline.

Non-Hydrated

Hydrated

Enquiry No.18
<table>
<thead>
<tr>
<th>Company/Website</th>
<th>Product and &quot;Partnerships&quot;</th>
<th>Available Configurations/Composition</th>
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<th>References</th>
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</thead>
<tbody>
<tr>
<td>Globus Medical</td>
<td>MicroFuse</td>
<td>Blocks with graft slots, granules, sheets / Fused Poly (Lactide-co-glycolide) and Poly (Lactic acid) microspheres</td>
<td>BVF</td>
<td>100% interconnected porosity, much stronger than standard porous ceramics, not brittle, will not crush when placed at the bone defect site, narrow pore size distribution (optimal for bone formation). Developed to be full resorbable implant with two polymers with different resorption profiles - resorption in 2 steps – with resorption of 1st phase, porosity increases and creates space for additional bone growth.</td>
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<tr>
<td>Grafys</td>
<td>Graftys BCP</td>
<td>Granules, sticks, cylinders, wedges, cones / 65% HA/35% β-TCP</td>
<td>BVF (extremities, spine and pelvis); also BVF in femoral or tibial osteotomies</td>
<td>Controlled resorption, 45% porosity for rapid bone ingrowth, rapid bone cell colonization at center of material (rapid bone ingrowth), stable and easy to use.</td>
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<tr>
<td>Integra LifeSciences</td>
<td>Mosaic/Osteoconductive Scaffold</td>
<td>Compression resistant strip and moldable putty / 40% high purity β-TCP; 20% high purity Type I collagen</td>
<td>BVF (extremities, spine and pelvis); also BVF in femoral or tibial osteotomies</td>
<td>Collagen surface of interconnected pores provides binding sites for osteoinductive agents. The same collagen has been used in over 10 million procedures and has a strong history of safety and biocompatibility. TCP provides defect filling volume and local mineral content. Product designed to resorb at a rate consistent with the formation of new bone. Available as a compression resistant strip and moldable putty.</td>
<td>Ingram R et al. Use of Integra Mosaic as a Bone Graft Substitute in the Rabbit Radius Segmental Defect. Data on file. Integra LifeSciences Corporation, Plainsboro, NJ. 2006.</td>
</tr>
<tr>
<td>ISTO Technologies</td>
<td>InQu</td>
<td>10cc and 30cc granules, 10cc paste/mix / Hyaluronic acid + poly (lactide-co-glycolide)</td>
<td>BVF (extremities and pelvis)</td>
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<tr>
<td>Kasios</td>
<td>Kasios TCP</td>
<td>Granules, blocks, rods; wedges / β-TCP</td>
<td>BVF</td>
<td>Highly bioactive; total or partial resorption; microporosity allows excellent osteointegration of granules.</td>
<td></td>
</tr>
<tr>
<td>LDR Spine</td>
<td>B+</td>
<td>2-3 mm irregular shape porous granules; blocks, cylinders, wedges, lipsers / 100% TCP</td>
<td>BVF (extremities, spine, and pelvis)</td>
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<tr>
<td>MedArtis</td>
<td>Synthacer</td>
<td>Blocks, cylinders, monolets, balls / Calcium phosphate ceramic with at least 95% HA</td>
<td>BVF (extremities, spine and pelvis)</td>
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</tr>
<tr>
<td>MedArtis</td>
<td>Syntricer</td>
<td>Blocks, cylinders, monolets, balls / Calcium phosphate ceramic with at least 95% HA</td>
<td>BVF (extremities, spine and pelvis)</td>
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<tr>
<td>Medical Biomat</td>
<td>Atlantik</td>
<td>Granules / 70% HA/30% β-TCP</td>
<td>BVF (extremities and pelvis)</td>
<td>Optimized porosity and surface to induce fast bone ingrowth and good osteointegration; interconnection of porostheses for cell penetration and increased contact with biological fluids.</td>
<td></td>
</tr>
<tr>
<td>Medicrea</td>
<td>Osmocys</td>
<td>Sticks/granules / 60% HA/40% β-TCP</td>
<td>BVF (extremities, spine and pelvis)</td>
<td>Excellent interconnected porosity compatible with human bone-cell size - allows the penetration of the fluids and the nutrients; excellent integration in both cortical and cancellous bone, new bone formation goes from surface to center of graft; macropores entirely filled by the bone.</td>
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Exhibit 1, continued on page 55
## FISCAL FITNESS

### Exhibit 1, continued from page 54

<table>
<thead>
<tr>
<th>Company/Website</th>
<th>Product and &quot;Partnerships&quot;</th>
<th>Available Configurations/ Composition</th>
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<tbody>
<tr>
<td>Medtronic</td>
<td>INFUSE Bone Graft</td>
<td>Putty / Recombinant human Bone Morphogenetic Protein-2 with an Absorbable Collagen Sponge (Part of BMP-2/MCS)</td>
<td>BMP approved for spinal fusion procedures in skeletally mature patients with degenerative disc disease at one level from L4-S1, should have had at least six months of nonoperative treatment. Also indicated for treating acute, open tibial shaft fractures that have been stabilized with IM nail fixation after appropriate wound management. Only bone graft substitute that provides proven and predictable bone growth and is backed by years of study and data.</td>
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<tr>
<td>Medtronic</td>
<td>Mastergraft</td>
<td>Granules, putty / 15% HA, 85% ß-TCP</td>
<td>BMP (posterolateral spine, pelvis, ilium and/or extremities); putty also as a bone graft extender (with autograft)</td>
<td>Made-up of 15% HA and 85% ß-TCP which provides 1) long term stability (not often found in comparable bone-void fillers) and 2) a consistent resorption rate. This consistent chemical and structural composition allows for a more predictable resorption rate.</td>
<td></td>
</tr>
<tr>
<td>Metries</td>
<td>K-Phate</td>
<td>Blocks, wedges, granules / 60% HA / 40% ß-TCP</td>
<td>BMP (extremities, spine and pelvis)</td>
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<td></td>
</tr>
<tr>
<td>Merries</td>
<td>Uni-Osteo</td>
<td>Calcium sulfate CaSO₄</td>
<td>BMP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NovaBone</td>
<td>BoneMedic and BoneMedic-S</td>
<td>Chips, blocks / trabecular HA w/o or w/o 1% silicon</td>
<td>BMP (extremities and pelvis)</td>
<td>Similar composition to mineral content of bone + macro/micro pores very similar to 3D structure of cancellous bone.</td>
<td></td>
</tr>
<tr>
<td>Novabone</td>
<td>Novabone; Distributed worldwide by MTF.</td>
<td>Putty, morsels / synthetic calcium phosphate-silicate (BioGlass) particulate</td>
<td>BMP (extremities and pelvis), also cleared for use of the term &quot;osteoclastic&quot;</td>
<td>Activity stimulates osteoclast proliferation and differentiation as evidenced during in vitro studies by increased levels of DNA synthesis and osteoclast markers. Supports higher level of osteoclast expression and activity. Bone growth observed throughout graft site, working outward from each individual particle, not just inward from host bone margins.</td>
<td></td>
</tr>
<tr>
<td>Nuvasive</td>
<td>Formagraft</td>
<td>Trabeculated fibrillar collagen + BMP-2/ceramic</td>
<td>BMP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olympus</td>
<td>Oferon</td>
<td>Blocks, cylinders, granules, wedges / T-BCP</td>
<td>BMP (extremities, spine and pelvis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthogena</td>
<td>Tripore HA, Tripore BP90 and Tripore BP15</td>
<td>Bags, granules / 100% HA, BP90 (90% HA/10% TCP), BP15 15% HA/85% ß-TCP</td>
<td>BMP (extremities and pelvis)</td>
<td>Royalty-free patented formula for bone tissue formation</td>
<td></td>
</tr>
<tr>
<td>Orthos</td>
<td>ØrIan</td>
<td>Granules / Highly pure β-TCP</td>
<td>BMP (long bones, extremities, spine and pelvis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthovita</td>
<td>VITOSSE Morsels</td>
<td>Pack (putty), strips, flow (extradisc) blocks, morsels, cartilage (filled cartilage), shapes / 100% β-TCP</td>
<td>BMP (spine, extremities and pelvis)</td>
<td>A robust human clinical data package prospective clinical studies showing equivalency to autograft. Optimized structure, porosity and chemistry - 90% porous, open and interconnected structure that guides the three-dimensional regeneration of bone, nano-sized particle building blocks enable cell mediated resorption as part of natural remodeling.</td>
<td></td>
</tr>
<tr>
<td>Orthovita</td>
<td>VITOSSE Foam; Manufactured by Kensey Nash.</td>
<td>Pack (putty), strips, flow (extradisc) blocks, morsels, cartilage (filled cartilage), shapes / 80% β-TCP, 20% Type I bovine collagen</td>
<td>BMP (spine, extremities and pelvis)</td>
<td>Same as for VITOSSE Morsels</td>
<td></td>
</tr>
<tr>
<td>Orthovita</td>
<td>VITOSSE Bioactive Foam; Manufactured by Kensey Nash.</td>
<td>Pack (putty), strips, flow (extradisc) blocks, morsels, cartilage (filled cartilage), shapes / 80% β-TCP, 20% Bioactive Glass, 20% Type I bovine collagen</td>
<td>BMP (spine, extremities and pelvis)</td>
<td>Same as for VITOSSE Morsels</td>
<td></td>
</tr>
<tr>
<td>Ossacure</td>
<td>Collos E</td>
<td>Granules / Equine type I collagen</td>
<td>BMP (extremities, spine and pelvis)</td>
<td>Regenerative and osteoconductive support, no risk of transmission of human pathogen germs, early ossification, easy to use.</td>
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Exhibit 1, continued on page 56
### Exhibit 1, continued from page 55

<table>
<thead>
<tr>
<th>Company/Website</th>
<th>Product and “Partnerships”</th>
<th>Available Configurations/Composition</th>
<th>Regulatory Status</th>
<th>Key Differentiation</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>OsteoMed</td>
<td>Injectable through syringe / After mixing the powder and liquid components of the product, it will turn into a low-crystalline hydroxyapatite, which is similar to the mineral phase of human bone.</td>
<td>BVF (spine, extremities and pelvis)</td>
<td>Increased tensile strength, increased flexural strength and increased fracture toughness (first cement to be drilled and screwed). Easy to mix and deliver. Sets in a wet environment and quinly in 5 minutes at 37°C. Cellular remodeling allows cement not to leave any gaps or voids as new bone forms in and around the implanted area in vivo.</td>
<td>39) OsteoVation EX Inject: Manufactured by Stryker in cranio-maxillofacial and podiatry markets.</td>
<td></td>
</tr>
<tr>
<td>OsteoTech</td>
<td>Blocks, cylinders, wedges, sheets and granules / Biocomposite of mineralized cortical fibres bound in a porous, resorbable poly (L-lactide-co-glycolide) scaffold</td>
<td>BVF (extremities and pelvis); recently filed for spine clearance and expects to hear very soon</td>
<td>Uunique in composition as it contains mineralized fibres encased in a resorbable polymer matrix. This combination provides a resilient scaffold able to withstand intra-operative contouring and handling. PLEXUR P forms (wedges, blocks, sheets and cylinders) are easily cut with a scalpel or rongeurs without crumbling and can be snapped when defects without altering upon impact.</td>
<td>39) OsteoVation EX Inject: Manufactured by Stryker in cranio-maxillofacial and podiatry markets.</td>
<td></td>
</tr>
<tr>
<td>PenRax</td>
<td>Powder, blocks / HA</td>
<td>BVF (extremities, spine and pelvis)</td>
<td>Reliably scaffold which becomes moldable upon heating and sets above body temperature. This versatil biocomposite is designed to produce a porous scaffold after manipulation and implantation.</td>
<td>39) OsteoVation EX Inject: Manufactured by Stryker in cranio-maxillofacial and podiatry markets.</td>
<td></td>
</tr>
<tr>
<td>Promed Advance</td>
<td>Calcium sulfate</td>
<td>BVF (extremities, spine and pelvis)</td>
<td></td>
<td>39) OsteoVation EX Inject: Manufactured by Stryker in cranio-maxillofacial and podiatry markets.</td>
<td></td>
</tr>
<tr>
<td>Stryker</td>
<td>Syringe + powder / injectable, scalable material / HA</td>
<td>BVF (extremities, spine, ilium and/or pelvis)</td>
<td>Fast setting, injectable or manual implantation; osteoconductive; excellent wet-field characteristics; osteoinductive, ability to augment provisional hardware</td>
<td>39) OsteoVation EX Inject: Manufactured by Stryker in cranio-maxillofacial and podiatry markets.</td>
<td></td>
</tr>
<tr>
<td>Stryker Biotech</td>
<td>OPL-I</td>
<td>Putty implant / Recombinant human bone/morphpogenic protein / with purified Type 1 collagen carrier</td>
<td>Approved under Humanitarian Device Exemptions for revision posterolateral lumbar spine fusion (puffy and for the treatment of long bone nonunion fractures (implant)</td>
<td>39) OsteoVation EX Inject: Manufactured by Stryker in cranio-maxillofacial and podiatry markets.</td>
<td></td>
</tr>
<tr>
<td>Syntheses</td>
<td>Injectable, fast-set putty / Calcium phosphate + dibut sodium phosphate</td>
<td>BVF (extremities and pelvis)</td>
<td>Isothermal hardening prevents thermal injury to the surrounding tissue, hardens in ~10 minutes in warm, wet environment (reducing the need to control moisture at the operative site), cures to maximum compressive strength of ~50MPa in 24 hours</td>
<td>39) OsteoVation EX Inject: Manufactured by Stryker in cranio-maxillofacial and podiatry markets.</td>
<td></td>
</tr>
<tr>
<td>Syntheses</td>
<td>Granules / βTCP + poly (lactide-co-ε-caprolactone)</td>
<td>BVF, also for posterolateral fusion w/ autogenous blood and/or bone marrow or autograft</td>
<td>39) OsteoVation EX Inject: Manufactured by Stryker in cranio-maxillofacial and podiatry markets.</td>
<td></td>
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</tbody>
</table>

**Exhibit 1, continued on page 57**
### Exhibit 1, continued from page 56

<table>
<thead>
<tr>
<th>Company/Website</th>
<th>Product and &quot;Partnerships&quot;</th>
<th>Available Configurations/Composition</th>
<th>Regulatory Status</th>
<th>Key Differentiation</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teknimed</td>
<td>Cementek</td>
<td>Liquid + powder injectable / TCP</td>
<td>BVF (extremities, spine and pelvis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teknimed</td>
<td>TriHA®</td>
<td>Granules, sticks / TCP</td>
<td>BVF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teknimed</td>
<td>Ceraform</td>
<td>Wedges, powders, granules, sticks, blocks / 65% HA/25% β-TCP</td>
<td>BVF (extremities, spine and pelvis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TriMed</td>
<td>Cross.Bone</td>
<td>Blocks, powders, syringe / 60% HA/40% β-TCP</td>
<td>Block, bottle and syringe for bone reconstructive surgery or as a bone filler (fractures or benign tumours/tumours)/ wedge for tibial osteotomy with internal fixation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zimmer</td>
<td>CapiCell Bone Void Filler</td>
<td>Sponge paste /BASIC calcium phosphate (67%) and Type I collagen (33%)</td>
<td>BVF (extremities, pelvis and spine)</td>
<td>Provides local supply of calcium and phosphate ions; provides acidic localized microenvironment which may preserve BMF solubility, available as a highly porous sponge (60% porous, pores 5 - 1000 µm) or high void volume paste; radiolucent; pliant and moldable when hydrated</td>
<td>Case reports and animal studies</td>
</tr>
</tbody>
</table>
Exhibit 2: Bone Graft Materials Available in the U.S.: DBM, Stem Cells and Xenograft

<table>
<thead>
<tr>
<th>Company/Website</th>
<th>Product and “Partnerships”</th>
<th>Available Configurations/Composition</th>
<th>Regulatory Status</th>
<th>Key Differentiation</th>
<th>For DBMs, what % of lots are tested for osteoinductive potential?</th>
<th>For DBMs, what type of sterilization / processing is used?</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aesculap Spine</td>
<td>ProSpace DBM</td>
<td>Putty, gel / Demineralized bone matrix (DBM) with reverse phase medium (RPM)</td>
<td>Bone graft extender (extremities, spine and pelvis) and BVF (extremities and pelvis)</td>
<td>Sample of each lot tested post sterilization in quantitative in vitro assay</td>
<td>E-Beam sterilization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AlloSource</td>
<td>Allofuse; Managed by IsoTis. However, due to changes in the licensing agreement, AlloSource will begin manufacturing it.</td>
<td>Putties, gels / 38% DBM with RPM</td>
<td>BVF, contains Human Cellular and Tissue Based Product (HCT/P) as defined in USDA 21 CFR Part 1271; Restricted to homologous use for the repair, replacement or reconstruction of musculoskeletal defects.</td>
<td>High DBM content; Reverse phase carrier has excellent handling properties; becomes stiffer when implanted, resistant to irrigation, and is not water soluble. Packaged sterile, incorporates the Sterile-R process, and is sterile according to USP standards.</td>
<td>Every lot tested for osteoinduction.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AlloSource</td>
<td>Allofuse Plus; Managed by IsoTis. However, due to changes in the licensing agreement, AlloSource will begin manufacturing it.</td>
<td>Putties, gels / 38% DBM with RPM &amp; cancellous chips</td>
<td>BVF, contains Human Cellular and Tissue Based Product (HCT/P) as defined in USDA 21 CFR Part 1271; Restricted to homologous use for the repair, replacement or reconstruction of musculoskeletal defects.</td>
<td>Same as for Allofuse.</td>
<td>Every lot tested for osteoinduction.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AlloSource</td>
<td>Osteocel: To be manufactured by AlloSource per an agreement with Osiris. Private labeled as Trinity. (See Orthofix.)</td>
<td>Formulation of cryopreserved cancellous chips, viable cancellous matrix, and ground bone matrix / Adult cadaveric stem cells with cancellous chips</td>
<td>HCT/P</td>
<td>Every lot tested for cell viability, quantity and quality.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altiva</td>
<td>Altiva DBM Manufacured by RTI Biologics.</td>
<td>Lyophilized room temperature powder / DBM w/or w/o cortical cancellous chips in gelatin carrier</td>
<td>BVF</td>
<td>All lots tested for quality and safety.</td>
<td>Terminally sterilized</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterin</td>
<td>OsteoSponge; Distributed by Innovasis, OrthoPro</td>
<td>Blocks, tiles / 100% human bone</td>
<td>HCT/P</td>
<td>Every lot tested for cell viability, quantity and quality.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterin</td>
<td>OsteoWrap</td>
<td>Thin sheath of cortical bone; can be rolled up, wrapped around or easily cut with a scalpel / 100% human bone</td>
<td>HCT/P</td>
<td>Every lot tested for cell viability, quantity and quality.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berkeley Advanced Materials</td>
<td>DBM</td>
<td>Putty, sponge, foam, sheets / DBM</td>
<td>BVF</td>
<td>Does not currently conduct osteoinductive testing on lots of Bonus.</td>
<td>End stage irradiation at 15-25 KGY with product packed in dry ice to preserve BMP activity. Also before demineralization, tissue processed with Allowash®, a patented bone and soft tissue cleaning technology under license from LifeNet.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Work is in progress to describe/evaluate the use of Bonus in grafting after core decompression for femoral head avascular necrosis and for grafting in bone cysts in a pediatric population. Currently there are no peer-reviewed references describing the use of Bonus.

*Exhibit 2, continued on page 59*
## Fiscal Fitness

**Exhibit 2, continued from page 58**

<table>
<thead>
<tr>
<th>Company/Website</th>
<th>Product and &quot;Partnerships&quot;</th>
<th>Available Configurations / Composition</th>
<th>Regulatory Status</th>
<th>Key Differentiation</th>
<th>For DBMs, what % of lots are tested for osteoinductive potential?</th>
<th>For DBMs, what type of sterilization / processing is used? *</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DePuy Spine</strong>&lt;sup&gt;2&lt;/sup&gt;&lt;br&gt;depuyacromed.com</td>
<td>OPTIMUM DBM; Manufactured by LifeNet Health; distributed by DePuy Orthopaedics and DePuy Spine.</td>
<td>BVF Powder + sterile saline - forms a putty-like consistency at room temperature; will flow or can be molded and packed into the defect, hardens and sets within 10 minutes of implantation. DBM powder + proprietary pure synthetic self-setting Nano-Crystalline Calcium Phosphate&lt;br&gt;For DBMs, what % of lots are tested for osteoinductive potential?</td>
<td>LifeNet Health’s largest bone bank in the U.S. and the first one accredited by AABB. (See <a href="http://www.lifenet.org">www.lifenet.org</a>.) Promotes donors through two patented technologies — Afflock, which removes 90% of bone marrow and blood elements, 40% more than through traditional methods; and PAD (Pulsed Accel Acoustic Disintegration), which controls residual calcium level for more consistent product. Greater osteoinductivity + optimal levels exceed AABB standard.</td>
<td>A representative sample of each lot of finished product is screened for osteoinductive potential in an in vitro assay and found to be osteoinductive. Osteoinductivity index (OI) score of greater or equal to one. Every lot is tested. (Osteoinductivity index (OI) be osteoinductive.</td>
<td>BVF, OPTIMUM DBM</td>
<td>1) Zhang M et al Effect(s) of the demineralization process on the osteoinductivity of deproteinized bovine bone matrix. J Periodontol 1998; 59(8): 958-961; 2) Turner AJ et al. The effects of residual calcium in calcified freeze-dried bone allograft in a critical-sized defect in the Rattus norvegicus calvarium. J Oral Maxillofac Surg 2002; 60(5): 555-62, 2006.</td>
<td></td>
</tr>
<tr>
<td><strong>DePuy Spine</strong>&lt;sup&gt;3&lt;/sup&gt;&lt;br&gt;depuyacromed.com</td>
<td>IC Graft Chamber; Manufactured by LifeNet Health; distributed by DePuy Orthopaedics and DePuy Spine.</td>
<td>BVF Powder + sterile saline - forms a putty-like consistency at room temperature; will flow or can be molded and packed into the defect, hardens and sets within 10 minutes of implantation / BVF Powder kit 1cc, 5cc, 10cc / BVF, OPTIMUM DBM&lt;br&gt;For DBMs, what % of lots are tested for osteoinductive potential?</td>
<td>LifeNet Health’s largest bone bank in the U.S. and the first one accredited by AABB. (See <a href="http://www.lifenet.org">www.lifenet.org</a>.) Promotes donors through two patented technologies — Afflock, which removes 90% of bone marrow and blood elements, 40% more than through traditional methods; and PAD (Pulsed Accel Acoustic Disintegration), which controls residual calcium level for more consistent product. Greater osteoinductivity + optimal levels exceed AABB standard.</td>
<td>A representative sample of each lot of finished product is screened for osteoinductive potential in an in vitro assay and found to be osteoinductive. Osteoinductivity index (OI) score of greater or equal to one. Every lot is tested. (Osteoinductivity index (OI) be osteoinductive.</td>
<td>BVF, OPTIMUM DBM</td>
<td>1) Zhang M et al Effect(s) of the demineralization process on the osteoinductivity of deproteinized bovine bone matrix. J Periodontol 1998; 59(8): 958-961; 2) Turner AJ et al. The effects of residual calcium in calcified freeze-dried bone allograft in a critical-sized defect in the Rattus norvegicus calvarium. J Oral Maxillofac Surg 2002; 60(5): 555-62, 2006.</td>
<td></td>
</tr>
<tr>
<td><strong>DePuy Spine</strong>&lt;sup&gt;3&lt;/sup&gt;&lt;br&gt;depuyacromed.com</td>
<td>Cellet Alograft Cartridge; Manufactured by LifeNet Health; distributed by DePuy Orthopaedics and DePuy Spine.</td>
<td>BVF Powder + sterile saline - forms a putty-like consistency at room temperature; will flow or can be molded and packed into the defect, hardens and sets within 10 minutes of implantation / BVF Powder kit 1cc, 5cc, 10cc / BVF, OPTIMUM DBM&lt;br&gt;For DBMs, what % of lots are tested for osteoinductive potential?</td>
<td>LifeNet Health’s largest bone bank in the U.S. and the first one accredited by AABB. (See <a href="http://www.lifenet.org">www.lifenet.org</a>.) Promotes donors through two patented technologies — Afflock, which removes 90% of bone marrow and blood elements, 40% more than through traditional methods; and PAD (Pulsed Accel Acoustic Disintegration), which controls residual calcium level for more consistent product. Greater osteoinductivity + optimal levels exceed AABB standard.</td>
<td>A representative sample of each lot of finished product is screened for osteoinductive potential in an in vitro assay and found to be osteoinductive. Osteoinductivity index (OI) score of greater or equal to one. Every lot is tested. (Osteoinductivity index (OI) be osteoinductive.</td>
<td>BVF, OPTIMUM DBM</td>
<td>1) Zhang M et al Effect(s) of the demineralization process on the osteoinductivity of deproteinized bovine bone matrix. J Periodontol 1998; 59(8): 958-961; 2) Turner AJ et al. The effects of residual calcium in calcified freeze-dried bone allograft in a critical-sized defect in the Rattus norvegicus calvarium. J Oral Maxillofac Surg 2002; 60(5): 555-62, 2006.</td>
<td></td>
</tr>
<tr>
<td><strong>Extex Corporation</strong>&lt;sup&gt;5&lt;/sup&gt;&lt;br&gt;etexcorp.com</td>
<td>EquiBone Powder + sterile saline - forms a putty-like consistency at room temperature; will flow or can be molded and packed into the defect, hardens and sets within 10 minutes of implantation / BVF Powder kit 1cc, 5cc, 10cc / BVF, OPTIMUM DBM&lt;br&gt;For DBMs, what % of lots are tested for osteoinductive potential?</td>
<td>LifeNet Health’s largest bone bank in the U.S. and the first one accredited by AABB. (See <a href="http://www.lifenet.org">www.lifenet.org</a>.) Promotes donors through two patented technologies — Afflock, which removes 90% of bone marrow and blood elements, 40% more than through traditional methods; and PAD (Pulsed Accel Acoustic Disintegration), which controls residual calcium level for more consistent product. Greater osteoinductivity + optimal levels exceed AABB standard.</td>
<td>A representative sample of each lot of finished product is screened for osteoinductive potential in an in vitro assay and found to be osteoinductive. Osteoinductivity index (OI) score of greater or equal to one. Every lot is tested. (Osteoinductivity index (OI) be osteoinductive.</td>
<td>BVF, OPTIMUM DBM</td>
<td>1) Zhang M et al Effect(s) of the demineralization process on the osteoinductivity of deproteinized bovine bone matrix. J Periodontol 1998; 59(8): 958-961; 2) Turner AJ et al. The effects of residual calcium in calcified freeze-dried bone allograft in a critical-sized defect in the Rattus norvegicus calvarium. J Oral Maxillofac Surg 2002; 60(5): 555-62, 2006.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exactech</strong>&lt;sup&gt;6&lt;/sup&gt;&lt;br&gt;exac.com</td>
<td>Optecure Lysylized Room Temperature Powder kit 1cc, 5cc, 10cc / BVF, OPTIMUM DBM&lt;br&gt;For DBMs, what % of lots are tested for osteoinductive potential?</td>
<td>LifeNet Health’s largest bone bank in the U.S. and the first one accredited by AABB. (See <a href="http://www.lifenet.org">www.lifenet.org</a>.) Promotes donors through two patented technologies — Afflock, which removes 90% of bone marrow and blood elements, 40% more than through traditional methods; and PAD (Pulsed Accel Acoustic Disintegration), which controls residual calcium level for more consistent product. Greater osteoinductivity + optimal levels exceed AABB standard.</td>
<td>A representative sample of each lot of finished product is screened for osteoinductive potential in an in vitro assay and found to be osteoinductive. Osteoinductivity index (OI) score of greater or equal to one. Every lot is tested. (Osteoinductivity index (OI) be osteoinductive.</td>
<td>BVF, OPTIMUM DBM</td>
<td>1) Zhang M et al Effect(s) of the demineralization process on the osteoinductivity of deproteinized bovine bone matrix. J Periodontol 1998; 59(8): 958-961; 2) Turner AJ et al. The effects of residual calcium in calcified freeze-dried bone allograft in a critical-sized defect in the Rattus norvegicus calvarium. J Oral Maxillofac Surg 2002; 60(5): 555-62, 2006.</td>
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*May/June 2008 • Orthopaedic Product News 59*

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Exhibit 2, continued on page 60
### Exhibit 2, continued from page 59

<table>
<thead>
<tr>
<th>Company/Website</th>
<th>Product and “Partnerships”</th>
<th>Available Configurations/Composition</th>
<th>Regulatory Status</th>
<th>Key Differentiation</th>
<th>For DBMs, what % of lots are tested for osteoinductive potential?</th>
<th>For DBMs, what type of sterilization / processing is used?</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exactech</strong> exac.com</td>
<td>Optifit; Manufactured by RTI Biologics.</td>
<td>Lyophilized Room Temperature Powder 2cc; 5cc; 10cc; 20cc; Frozen Desiccated 2cc; 5cc; 10cc; 20cc; 21cc; 30cc; 50cc / 60% by weight DBM, densely packed cortical cancellous chips in a collagen carrier</td>
<td>BVF (extremities, spine and pelvis)</td>
<td>1. Very resistant to lavage. 2. Becomes resilient at body temperature. 3. Dry storage maintains bioactivity of the bone forming proteins and allows surgeons to hydrate with autologous diuretics. 4. Conducive lattice of cortical and cancellous bone addresses the mechanical prompt to bone formation. Cortical bone provides for compressible strength and cancellous bone provides a porous environment for cell attachment. 100% in vivo. Every donor is tested using the Unit athermic nude rodent model. Explants are evaluated through histo and scored for actual bone content. Donors must meet minimum criteria for acceptance.</td>
<td>Terminal Sterilized</td>
<td>1) Philips GA, et al. Efficacy of Composite Allograft and Demineralized Bone Matrix (DBM) Graft in the Treatment of Tibial Plateau Fractures with Bone Loss. Presented at WDA 2007; 2) Roukis T. Use of an Osteoinductive/Osteoconductive Bone Allograft for Revision of Failed and/or Ankle Arthroplasty Non-union/Malunion Deformities in the High-risk Patient. Presented at AOFAS 2005.</td>
<td></td>
</tr>
<tr>
<td><strong>Exactech</strong> exac.com</td>
<td>Optifit; Manufactured by RTI Biologics.</td>
<td>Lyophilized Room Temperature Powder 1cc; 5cc; 10cc; 15% by weight DBM in a collagen carrier</td>
<td>BVF (extremities, spine and pelvis)</td>
<td>1. Very resistant to lavage. 2. Becomes resilient at body temperature. 3. Dry storage maintains bioactivity of the bone forming proteins and allows surgeons to hydrate with autologous diuretics. Same as for Optifit.</td>
<td>Same as for Optifit.</td>
<td>Women, JF et al. Effect of bone protein and carrier matrices on BMP-stimulated osteogenesis. The 44th Annual Meeting of the Orthopaedic Research Society.</td>
<td></td>
</tr>
<tr>
<td><strong>Integra Life Sciences</strong> integra-ls.com</td>
<td>Accell 100</td>
<td>Putty / DBM</td>
<td>BVF (extremities and pelvis); bone graft extender spine, extremities and pelvis</td>
<td>Osteoconductive, osteoinductive potential and bioresorbable</td>
<td>100%</td>
<td>E-Beam sterilization</td>
<td></td>
</tr>
<tr>
<td><strong>Integra Life Sciences</strong> integra-ls.com</td>
<td>Accell TBM</td>
<td>Preformed scaffold/ matrix / Preformed Total Bone Matrix made from DBM</td>
<td>BVF (extremities and pelvis); bone graft extender spine, extremities and pelvis</td>
<td>Osteoconductive, osteoinductive potential and bioresorbable</td>
<td>Osteoconductive, osteoinductive potential and bioresorbable</td>
<td>Same as for Accell 100</td>
<td></td>
</tr>
<tr>
<td><strong>Integra Life Sciences</strong> integra-ls.com</td>
<td>Accell Connexus</td>
<td>Putty / DBM in RPM</td>
<td>BVF (extremities and pelvis); bone graft extender spine, extremities and pelvis</td>
<td>Osteoconductive, osteoinductive potential and bioresorbable</td>
<td>Osteoconductive, osteoinductive potential and bioresorbable</td>
<td>Same as for Accell 100</td>
<td></td>
</tr>
<tr>
<td><strong>LifeCell</strong> lifecell.com</td>
<td>AlloCraft DBM; DBM processed by LifeLink Tissue Bank. Acellular Dermal Matrix processed by LifeCell Corporation. Product distributed by Skyler Spine.</td>
<td>Putty / 100% human tissue comprising 80% DBM (by volume) and 20% human acellular regenerative matrix</td>
<td>BVF</td>
<td>The carrier, an acellular human tissue matrix, supports rapid cellular repopulation and revascularization which along with the DBM yields new bone formation more rapidly than autologous bone</td>
<td>100% of lots are tested for osteoinductive potential in an in vivo animal model by a GLP laboratory.</td>
<td>Passes sterility testing as defined by USP71.</td>
<td></td>
</tr>
<tr>
<td><strong>Medtronic</strong> sofamorandak.com</td>
<td>OsteoLife Allograft Paste; Processed by RTI Biologics.</td>
<td>Allograft paste; available in frozen and room temperature forms / DBM with porcine gelatin carrier</td>
<td>BVF (extremities, spine and pelvis)</td>
<td>Processed using the Biocleanse system which ensures sterility, which is a common concern when using cadaver tissue.</td>
<td>100% of lots are tested for osteoinductive potential</td>
<td>Level of sterilization is 10-6</td>
<td></td>
</tr>
<tr>
<td><strong>Medtronic</strong> sofamorandak.com</td>
<td>Progenesis DBM Putty</td>
<td>Putty / 70% DBM in a biocompatible carrier which is a mixture of bovine collagen (Type I bovine-collagen) with a natural polysaccharide (sodium alginate) to enhance handling properties</td>
<td>BVF and bone graft substitute (putty, bum and extremities) used alone in extremities or pelvis; must be mixed with autograft bone and used as a bone graft extender in spine. Firm, yet moldable putty consistency that resists dissolution and can be delivered precisely through a syringe; no other DBM on the market offers the complete package of handling characteristics like PROGENIX™ DBM Putty.</td>
<td>100% of lots are tested for osteoinductive potential. Certified osteoinductive through a validated, osteoinductive assay on initial DBM and final sterilized DBM product. To mitigate variability and ensure consistent osteoinductive performance.</td>
<td>Same as for OsteoLife</td>
<td>1) Qui QQ et al. Bone Formation in Calvarial Defects by CBM/MAM Composite. Journal of Biomedical Material Research 81B: 516-523, 2007; 2) Qui QQ et al. Evaluation of AlloCraft®-DBM Putty as a Graft Substitute for Spinal Fusion. Journal of Biomedical Material Research 82B: 239-245, 2007.</td>
<td></td>
</tr>
</tbody>
</table>

---

**References**

### OrthoFix

**Company/Website**: orthofix.com  
**Product and “Partnerships”**: Osteogen DBM with Bioactive Glass  
**Regulatory Status**: Approved by the U.S. Food and Drug Administration  
**Key Differentiation**: Contains Bioactive Glass, which is a unique synthetic material that is extremely biocompatible and resists movement under irrigation, high quality donor tissue, biocompatible and biological origin, easy to use (no mixing or thawing)  

### Osteotech

**Company/Website**: osteotech.com  
**Product and “Partnerships”**: DBM graft  
**Regulatory Status**: Approved by the U.S. Food and Drug Administration  
**Key Differentiation**: Holds the largest Burden of Proof of all DBMs, having prospective human clinical published trials. Only DBM shown as effective an autograft as a substitute product in postero-lateral fusion. Most osteoinductive DBM due to demineralized bone fibers which are patented by Osteotech. Highest osteoinductive DBM due to superior processing  

### Smith & Nephew

**Company/Website**: smith-nephew.com  
**Product and “Partnerships”**: ViGraf DBM  
**Regulatory Status**: Approved by the U.S. Food and Drug Administration  
**Key Differentiation**: Comes in five forms, assuming the surgeon has the right form for the bone graft procedure being performed, proven osteoinductive 100% of the time in animal trial conducted with the treated product. Multiple pack sizes provide customer savings by reducing waste. No preparation required  
### Exhibit 2, continued from page 61

<table>
<thead>
<tr>
<th>Company/Website</th>
<th>Product and “Partnerships”</th>
<th>Available Configurations/Composition</th>
<th>Regulatory Status</th>
<th>Key Differentiation</th>
<th>For DBMs, what % of lots are tested for osteoinductive potential?</th>
<th>For DBMs, what type of sterilization / processing is used?</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spineology</strong></td>
<td></td>
<td>AFT in sodium hyaluronate carrier; Dry Mix / Granular Graft mixtures of DBM + corticocancellous chips</td>
<td>BVF</td>
<td>Handling better than other DBM putties...moving in O.R. allows addition of equal volumes of BMA without loss of handling</td>
<td>All are tested for osteoinductivity (either the final product and/or the DBM) - 100%</td>
<td>All lots are sterilized with e-beam irradiation for sterility</td>
<td>Wilkins K. The Effect of ALLOMATRIX® Injectable Putty on the Outcome of Long Bone Applications. Orthopedics 26(5): s567-s570, 2003</td>
</tr>
<tr>
<td><strong>Wright Medical</strong></td>
<td>Ailmatrix</td>
<td>Putty / DBM (w/ w/o cancellous chips) + CaSO₄ carrier</td>
<td>BVF</td>
<td>Only DBM composite designed specifically to address problem fractures minimally invasively</td>
<td>All are tested for osteoinductivity (either the final product and/or the DBM) - 100%</td>
<td>All lots are sterilized with e-beam irradiation for sterility</td>
<td>Wilkins et al. Percutaneous Treatment of Long Bone Nonunions: The Use of Autologous Bone Marrow and Allograft Bone Matrix. Orthopedics 26(5): s549-s554, 2003</td>
</tr>
<tr>
<td><strong>Wright Medical</strong></td>
<td>Ignite</td>
<td>Injectable when mixed with appropriate volume of BMA / DBM + CaSO₄ carrier (designed to be rehydrated with BMA)</td>
<td>BVF</td>
<td>As strong as allograft cancellous bone and readily available off-the-shelf as a sterile implant</td>
<td>All are tested for osteoinductivity (either the final product and/or the DBM) - 100%</td>
<td>All lots are sterilized with e-beam irradiation for sterility</td>
<td>Wilkins et al. Percutaneous Treatment of Long Bone Nonunions: The Use of Autologous Bone Marrow and Allograft Bone Matrix. Orthopedics 26(5): s549-s554, 2003</td>
</tr>
<tr>
<td><strong>Wright Medical</strong></td>
<td>Cancelllo-Pure</td>
<td>Wedges / Bovine cancellous bone</td>
<td>BVF</td>
<td>Provides expanded supply of safe, sterile tissue. Studies show CopiOs Cancellous Bone Graft incorporates (remodels) comparably to allograft</td>
<td>Ready-to-use DBM stored at controlled room temperature; every lot tested using an in vivo rat assay. Final (packaged, sterilized) product tested for osteoinductive potential using an in vivo rat assay. Sterilized to SAL 10-6 using low dose, “cold” gamma irradiation</td>
<td>Case reports and animal studies</td>
<td></td>
</tr>
<tr>
<td><strong>Zimmer</strong></td>
<td>Puros® Demineralized Bone Matrix</td>
<td>Putty / 100% derived from allograft tissue - including carrier</td>
<td>BVF</td>
<td>Provides expanded supply of safe, sterile tissue. Studies show CopiOs Cancellous Bone Graft incorporates (remodels) comparably to allograft</td>
<td>Ready-to-use DBM stored at controlled room temperature; every lot tested using an in vivo rat assay. Final (packaged, sterilized) product tested for osteoinductive potential using an in vivo rat assay. Sterilized to SAL 10-6 using low dose, “cold” gamma irradiation</td>
<td>Case reports and animal studies</td>
<td></td>
</tr>
</tbody>
</table>

### Notes to Exhibit 2:
* A side from testing of donor tissue and determination of eligibility of tissue for transplantation by qualified tissue bank.

Shirley A. Engelhardt is President and Founder of Knowledge Enterprises, Inc., a strategic services firm solely focused on orthopaedics. She is also a Founder and Managing Member of Knowledge Ventures, LLC, an early stage musculoskeletal investment fund. She can be reached at 336-685-5448 or shirley@orthoworld.com.

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May 2008

May 1-3
American Orthopaedic Foot & Ankle Society Advanced Foot and Ankle Course
San Francisco, CA
www.aofas.org

May 5
RRY Publications 3rd Annual Spine Technology Summit
Miami, FL
www.ryortho.com/2008spine

May 6-9
Spine Arthroplasty Society Global Symposium on Motion Preservation Technology, 8th Annual Meeting
Miami, FL
www.spinearthroplasty.org

May 16-17
Orthopaedic Trauma Association Advanced Trauma Techniques Course for Residents
Dallas, TX
www.ota.org

May 18-21
Current Concepts in Joint Replacement Spring Meeting
Las Vegas, NV
www.ccjr.com

May 19-20
Rodman & Renshaw 5th Annual Global Healthcare Conference
Monte Carlo, Monaco
www.rodmanandrenshaw.com

May 19-20
Winston-Salem, NC
www.cednc.org

May 21-24
European Society of Sports Traumatology, Knee Surgery & Arthroscopy Annual Meeting
Porto, Portugal
www.seskra.org

May 25-31
The International Society for the Study of the Lumbar Spine Annual Meeting
Geneva, Switzerland
www.islsls.org

May 26-31
Spine Society of Europe: SpineWeek
Geneva, Switzerland
www.spineweek.com

May 28-31
American College of Sports Medicine Annual Meeting
Indianapolis, IN
www.acsm.org

May 28-June 1
8th World Biomaterials Congress
Amsterdam, The Netherlands
www.wbc2008.com

May 29-June 1
European Federation of National Associations of Orthopaedics & Traumatology 9th EFORT Congress
Nice, France
www.efort.org

May 30-31
6th Annual Medical Innovations Conference, Hosted by Materialise
Vienna, Austria
www.materialise.com

June 2008

June 3-7
1st World Congress of Minimally Invasive Spine Surgery & Techniques
Honolulu, HI
www.wcmisst.org

June 4-7
American Orthopaedic Association Annual Meeting
Quebec, Canada
www.aoassn.org

June 11-14
Southern Orthopaedic Association Annual Meeting
Hot Springs, VA
www.soaassn.org

June 12-14
European Society of Musculoskeletal Radiology Annual Meeting
Galway, Ireland
www.esmr.org

June 13-14
AAOS Continuing Medical Education Course #3207
AAOS/POSNA Surgical Techniques for Managing Pediatric Orthopaedic Sports Injuries
Rosemont, IL
www.aaos.org

June 13-17
Association of Bone and Joint Surgeons Annual Meeting
Jackson Hole, WY
www.abjs.org

June 17-19
Medtech Insight’s In3 Medical Device Summit Annual Meeting
San Francisco, CA
www.meddevicesummit.com

June 18-19
Fourth Annual Orthopaedic Manufacturing & Technology Exposition and Conference (OMTEC)
Rosemont, IL
www.orthosupplier.com

June 19-22
American Spinal Injury Association Annual Meeting
San Diego, CA
www.asia-spinalinjury.org

June 25-28
American Orthopaedic Foot & Ankle Society 24th Annual AOFAS Summer Meeting and Pre-meeting Course
Denver, CO
www.aofas.org

July 2008

July 8-11
Scoliosis Research Society - IMAST: International Meeting on Advanced Spine Techniques
Hong Kong, China
www.imastonline.com

July 10
AAOS Continuing Medical Education Course #3230
AAOS/ASSH General Orthopaedic Review
Chicago, IL
www.aaos.org

July 10-13
American Orthopaedic Society for Sports Medicine Annual Meeting
Orlando, FL
www.sportsmed.org
July 13-15
International Society for Fracture Repair Biennial Meeting
Lake Tahoe, NV
www.fractures.com

July 18-19
AAOS Continuing Medical Education Course #3206
AAOS/ASES Arthroscopic Management of Rotator Cuff Disease and Instability
Rosemont, IL
www.aaos.org

July 23-26
Western Orthopaedic Association Annual Meeting
Maui, HI
www.woa-assn.org

August 2008

August 24-28
International Society of Orthopaedic Surgery and Traumatology - SICOT/SIROT 2008 XXIV Triennial World Congress
Hong Kong, China
www.sicot.org

September 2008

September 9-13
Scoliosis Research Society Annual Meeting & Course
Salt Lake City, UT
www.srs.org

September 10-12
Clinical Orthopaedic Society Annual Meeting
Point Clear, AL
www.cosociety.org

September 11-13
Society for Biomaterials - Translational Biomaterial Research: Advancing Discoveries from the Laboratory to the Clinic
Atlanta, GA
www.biomaterials.org

September 15-16
American Institute for Medical and Biological Engineering Council of Societies’ 3rd Annual Federal Symposium
Washington, D.C.
www.aimbe.org

September 17-20
The 7th Annual SIGN Conference (Surgical Implant Generation Network)
Richland, WA
www.sign-post.org

September 18-20
AAOS Continuing Medical Education Course #3210
Contemporary Techniques in Spinal Surgery 2008
Rosemont, IL
www.aaos.org

September 18-20
American Society for Surgery of the Hand 63rd Annual Meeting
Chicago, IL
www.assh.org

September 18-20
International Federation of Foot and Ankle Societies Third Triennial Scientific Meeting
Bahia, Brazil
www.globalfoot.org

September 18-21
Osteoarthritis Research Society International Annual World Congress on Osteoarthritis
Rome, Italy
www.oarsi.org

September 20
AAPS Continuing Medical Education Course #3232
Top Orthopaedic Controversies
Irvine, CA
www.aaos.org

September 21-24
Washington, DC
www.advamed2008.com

September 25-27
Clinical Orthopaedic Society Annual Meeting
Annapolis, MD
www.cosociety.org

September 26-27
Orthopaedic Rehabilitation Association Annual Meeting
Seattle, WA
www.orthorehabassoc.org

October 2008

October 10-12
AAOS Continuing Medical Education Course #3228
AAOS presents Life After Orthopaedics: Prepare for Career Changes and Retirement
Tucson, AZ
www.aaos.org

October 11-15
2008 BIO Venture Capital Forum: Invest in Biotechnology, Invest for Future
Dalian, China
www.bio-vc.com

October 14-18
North American Spine Society 23rd Annual Meeting
Toronto, Canada
www.spine.org

October 16-18
Orthopaedic Trauma Association Annual Meeting
Denver, CO
www.ota.org

October 17-19
AAOS Continuing Medical Education Course #3227 - 3rd Annual Orthopaedic Practice Management Course: Building Essential Skills for a Successful Practice
Washington, D.C.
www.aaos.org/education/mastcaldb/cme.cfm

October 22-24
Medtech Insight’s Investment in Innovation (In3) East
Boston, MA
www.medtechinsight.com

October 22-25
Eastern Orthopaedic Association Annual Meeting
Henderson, NV
www.eoa-assn.org
ABSTRACT

Objective: This study was performed to collect five-year follow-up on patients with lumbar disc herniation treated with intradiscal injection of ozone gas.

Background: Disc herniation is the most common cause for spinal surgery, and many clinicians employ epidural steroid injections with limited success. In numerous countries, intradiscal injection of ozone gas has been used as an alternative to epidural steroid and surgical discectomy. Early results are positive, but long-term data are limited.

Methods: Ninety-five patients with confirmed contiguous disc herniation were treated with intradiscal injection of ozone in 2002. Eighty-seven patients were available for telephone follow-up at five years and a chart review was performed. Patients were asked to describe their clinical outcome since the injection. Surgical interventions were documented. Available MRI films were collectively reviewed to assess the reduction in disc herniation at six months.

Results: Of the 87 responders at five years, 63 (72%) reported being “much better,” three (3%) were “better,” eight (9%) had no improvement and 13 (15%) went on to surgery. There were 12 discectomies and one fusion, with ten of the 13 surgeries occurring within the first year. Two patients had a second intradiscal ozone injection for an average of 1.02 injections per patient. MRI films demonstrated a consistent reduction in the size of the disc herniation. Seventy-nine percent of patients had a reduction in herniation volume and the average reduction was 56%. Other than subsequent surgeries typically associated with these patients, no complications were experienced.

Conclusion: Ozone is a conservative alternative to surgical discectomy for many patients. The gas reduced the size of the disc herniation. Randomized trials are required to gain wider acceptance of this treatment option.

INTRODUCTION

Disc herniation is the most common cause of lumboradicular pain and is the most frequent indication for spine surgery. The yearly incidence rate of disc herniation in the U.S. has been reported to be 1.7%. From 1990 to 1993, 0.8% of the population of the state of Washington had first time surgery for disc herniation annually. The rate of reoperation is between seven to nine percent at two years, and increases up to 25% at ten years postoperative. Patients with extensive epidural scarring are three times or more likely to experience recurrent radiculopathy than those with less extensive epidural scarring.

Conservative care should be exhausted prior to surgery. It is estimated that in 2007, there were over one million U.S. patients in conservative care for disc herniation and an additional 245,000 opting for surgery. In the Medicare population, the annual rate of epidural injections is 2,055 per 100,000 patients. Nine percent of those were for a diagnosis of herniated disc and 33% were for radiculopathy. Steroid injections have a transient effect and the average number of injections received by a patient was 2.5. Assuming a population of 300 million, approximately 222,000 U.S. patients are undergoing steroid injection each year specifically for disc herniation, and an additional 813,000 for radiculopathy. Approximately 25% to 47% of patients having epidural steroid injections for disc herniation go on to surgery.

Intradiscal injection of ozone (O3) gas was first proposed in the 1980s as a treatment for disc herniation. Ozone is a tri-atomic form of oxygen that can be created through corona discharge or ultraviolet light. Ozone has a half-life of approximately 45 minutes at ambient conditions, reverting back to oxygen, and therefore must be produced onsite for immediate injection. Ozone is a strong oxidizer and its application to the nucleus results in cleaving of the proteoglycan molecules and neutralization of the negatively charged sulfate side chains. This likely reduces the disc’s ability to retain water and may result in a reduction of the herniation volume. Additionally, ozone may initiate a biological cascade to reduce inflammation associated with the herniated material.

Several animal studies involving spinal application of ozone have been reported in the literature. These include dose response studies in rabbits, an acute toxicity study in pigs, and a veterinary application continued on page 67
continued from page 66

to dogs presenting with paraesthesia or paralysis due to disc herniation.22 These studies support that ozone has a dose-related response involving changes to the collagen fibrils and nuclear cells. Ozone had no toxic effect when injected into the epidural space of pigs. Canines treated with ozone demonstrated improved function that was maintained out to 18 months.

Several clinical reports of the use of ozone to treat lumbar23, 24, 25, 26, 27, 28, 29, 30, 31, 32 and cervical33, 34 disc herniations in humans have been presented in the literature. Only one randomized, blinded trial has been reported, but there are numerous non-randomized prospective and retrospective studies in the literature. Authors consistently report success rates between 65 to 80% and few complications. There are isolated case reports involving adverse events following intradiscal injection of ozone. These include a case of transient bilateral blindness following a large injection of ozone35, a nerve root injury associated with a pressure spike during the injection36, a thunderclap headache attributed to puncture of the thecal sac37, and a fatal septicemia due to E. Coli infection.

Here we report a retrospective long-term analysis of 94 patients sequentially treated with ozone chemonucleolysis. Six month postoperative MRI and 5 year postoperative clinical data are presented.

METHODS

Demographics: From January 2002 through January 2003, 94 patients (40 females, mean age 44.9 ± 14.5 years) were treated with percutaneous ozone chemonucleolysis. All patients suffered radicular leg pain and some reported additional back pain. The duration of symptoms was at least one month (mean 9.2 ± 15.4 months and median four months) and patients were non-responsive to conservative treatment modalities. None of the patients submitted to the treatment presented motor palsy of Fisher < 4. In all cases, MRI was used to confirm a protruded or extruded disc/s between L2 and S1. There were 77 patients with single level involvement, 15 with two levels and two with three levels. Patients that presented with signs of motor palsy (Fisher < 4), low back pain as the only symptom, sequestrated (free) disc fragments or other spinal pathologies such as tumours, lyses, fractures, severe stenosis and previous surgical surgeries, were not treated with ozone and are therefore not included in the study. All patients gave informed consent.

Procedure: The procedure was performed in the operating room under moderate sedation. The patient was prepared by the anaesthesiologist with pharmacological sedation half an hour before the procedure and then brought to the operating room and positioned in lateral decubitus leaving the affected side upwards with the hips and knees flexed in the fetal position. The operating table was adjusted to assume a convex shape, allowing the surgeon easier access to the disc. After standard antiseptic prepping and sterile draping, a Chiba-type needle (18 G, 27 cm long) was introduced by the standard postero-lateral, extra-articular percutaneous approach. The side of approach corresponded to the side of maximal pain as described by the patient. This corresponded to the side of disc herniation as seen on the MR images in 97% of patients. The gas disperses throughout the disc and annular tears so the side of approach is not believed to be critical. All procedures were performed under fluoroscopic control. AP and lateral imaging confirmed the position of the needle within the disc. The needle tip was situated centrally inside the nucleus pulposus.

The ozone-oxygen mixture was produced in real-time by a medical ozone generator (Ozonline E 80, Medica srl, Bologna Italy). The concentration of the gas mixture was approximately 40 mg O3/ml O2 and a quantity ranging between 5 to 10 ml were injected into each level. Between the syringe and the needle, a bacteriological Millipore filter was positioned before infiltrating the gas mixture inside the disc space. The ozone-oxygen mixture was released inside the disc space at an approximate rate of 10 ml/min. The gas mixture inside the disc space was visible on fluoroscopy. Gas was observed diffusing through the disc space and through the herniation. The patient was kept for overnight observation and discharged the next morning. Return to work was permitted seven days after the procedure. The mean operating time was 15 minutes (range: eight to 20 minutes).

Clinical Assessment: Patient history, demographic and clinical data were collected from hospital records and a confidential computer database maintained by the investigator. An independent assessor performed a telephone interview and the patients were asked the following questions:

• How do you feel with respect to the pre-operative clinical status: worse, unchanged, better, much better?
• Have you had any recurrences of the pain during the five year period?
• Do you use pain killers: never, occasionally, on a regular basis?

Fifty-three patients had an MRI at six months follow-up (range three to eight months). Images were evaluated by independent neuroradiologists and compared to the preoperative images. The change in the herniation volume was recorded in AP and lateral views.

RESULTS

Clinical Assessment: Eighty-seven patients (93%) were available for telephone interview. Results are summarized in Exhibit 1. In total 67 patients (76%) reported a durable improvement over five years following intradiscal ozone injection. Twenty patients (24%) did not achieve or maintain the improvement for five years. Twelve patients had discectomy and one patient had a fusion within five years for a surgery rate of 15%. Two of the 87 patients had a second ozone injection for an average of 1.02 injections per patient.

Exhibit 1: Results summarized over a five-year period. This graph includes all 87 patients available for follow-up. Seven patients could not be located.

Results over 5 years

continued on page 68
Compared to preoperative status, three patients reported feeling “better” and 63 reported feeling “much better.” The three patients in the “better” group reported absence of pain but some degree of occasional tingling in the leg related to posture. They reported occasional use of painkillers and one patient reported performing postural exercises twice a year for persisting back pain. Six patients in the group reporting as “much better” experienced worsening of symptoms for a period of time ranging between one to three weeks that was treated with NSAIDs and physical therapy, mainly postural exercises. These events occurred between two to four years after the initial treatment. Two of these patients reported two to three isolated events of pain in the past five years. The patient that went on to fusion had an improvement in leg pain but developed back pain between three and four months. Conservative care was employed for eight months before the fusion was performed.

Of the 21 patients (24%) who reported an “unchanged” or “worse” status, 15 patients reported having never obtained any clinical improvement after the procedure. Of these 15 patients, eight went on to microdiscectomy one to four months after the ozone procedure. The remaining seven patients continue to be treated with conservative means and occasional pain medication. Three patients maintained improvement for approximately one year and then worsened: one was operated upon, one repeated the ozone chemonucleolysis and one refused surgery and is on pain medication. Two patients maintained benefit for two years before experiencing a recurrence of pain that required microdiscectomy. Two patients maintained clinical improvement for three years and then worsened: one went on to microdiscectomy and had a second injection of ozone.

Chi-square analysis was performed to determine if disc level or number of disc levels was predictive of clinical success. Patients were divided into those that improved (better or much better) and not improved (no improvement or worse). There was no significant difference in clinical outcome between single level cases and multiple level cases ($\chi^2=1.81$, dof=1, $p=0.18$). Isolating the single level cases and testing for effects of disc level revealed no significant relationship ($\chi^2=1.48$, dof=3, $p=0.688$).

The mean preoperative symptom duration for the non-improved group was 12.5 (± 22.7, n=20) months compared to 8.8 (± 13.4, n=67) months for the group of improved patients. This was not statistically significant ($p=0.37$)

Radiographic Assessment: The post-operative MRI review of 53 patients revealed significant changes compared to pre-op in 42 patients (79%). The reduction in herniation volume ranged between 50 to 100% (mean 56.1%). See Exhibit 2 for a typical result. Exhibit 3 shows the pre- and post-MRIs for the patient who went on to fusion. The film demonstrates some collapse of the disc that resulted in back pain several months after the injection of intradiscal ozone.

With the exception of the single case of disc collapse that resulted in a fusion and previously described discectomies, no other complications were observed. Specifically, there were no cases of discitis, septicemia, blindness, headache, cerebrospinal fluid fistulae, etc.

**DISCUSSION**

Ozone chemonucleolysis for disc herniations has been performed for 20 years in countries such as Italy, India, Spain, Germany, Argentina, Korea and China. The authors are only aware of one other report of five-year follow-up following intradiscal injection of ozone.29 That study reported on an aggregated 6,665 patients treated in Italy, Spain and Argentina. All patients had a disc herniation that was unresponsive to conservative care such as physical therapy and medication. These patients were treated with intradiscal ozone followed by four paramuscular injections rather than a single intradiscal injection, as in this report. These authors reported complete elimination of pain in 80%, improvement in 12% and no improvement in seven percent. That study, like this one, lacks randomization and blinding. However, both confirm durable positive results in a large percentage of patients without surgery.

Two questions arise from the lack of randomized control trials. Are the results related to a placebo effect, or simply evidence of the natural history of disc herniation? Gallucci et al.23 reported the results of a randomized, blinded study of 159 patients assigned to either ozone combined with steroids or steroids alone. At two weeks the results between groups were equivalent, likely due to the short-term affect of steroids and anesthetic. At three months, however, results began to diverge but were not significant. At six months, 74% of the patients with ozone reached an ODI score of less than 20%, whereas only 47% of the steroid-treated group reached this level of improvement.

**Exhibit 2:** MRI showing a reduction in the volume of the disc herniation after intradiscal ozone injection. The follow-up MRI was taken at five months.

**Exhibit 3:** MRI showing the pre- and six-month MRI films of the patient that went on to fusion. This patient improved in their leg pain but developed back pain between four to six months.
Muto et al. reported on 2,200 patients treated with intradiscal ozone and followed for 24 months. A group of patients were treated including degenerative disc disease complicated with disc herniation, isolated herniation, failed back syndrome, calcified disc herniations and disc herniation associated with stenosis. Ozone injection was most effective in cases with single level disc herniations (64% Excellent and 14% Good or Fair) and the effectiveness decreased with disc degeneration (40% Excellent, 39% Good or Fair), calcified disc herniations (34% Excellent, 19% Good or Fair) and disc herniation with stenosis (25% Excellent, 25% Good or Fair). With all indications, maximum improvement was at six months and the results were stable to 18 months. If the placebo effect was solely responsible for the benefit, then there would not be such a difference in the outcome based on the indication.

In an effort to study the natural history of disc herniation, several authors have attempted to compare conservative management to surgery. The results have been equivocal. There are significant challenges in designing randomized trials comparing non-surgical and surgical treatment for disc herniation, particularly cross-over between assigned groups. These studies indicated, per an intent-to-treat analysis, that there was no significant difference between conservative and surgical treatment after one to two years. The surgical treatment offered more immediate benefit, but the results equalize over time. The amount of crossover between groups confirmed that patients with wide array of symptoms are apt to demand surgery, while those with less severe symptoms are prone to delay surgery. Patients appear well suited to balance the risk and benefit of their treatment options.

We observed that out of 53 randomly selected patients performing a control MRI after the treatment, 42 patients (79%) showed regression of the herniation volume of approximately 56%. All of these patients had a significant clinical improvement. Other authors have also reported that the disc herniation volume is not always correlated with clinical symptoms and that the persistence of herniation may not be correlated with the worsening of clinical status. Asymptomatic patients with positive CT scans for disc herniation are not a rare event.

The biochemical component of the disc degeneration is an important source of pain that is coupled with nerve root compression. Recently, laboratory results showed that epidural application of autologous nucleus pulposus can induce pronounced morphological and functional changes in nerve roots due to an increase in endoneurial fluid pressure and a decrease of blood flow in the dorsal root ganglia with resulting concomitant increase in its excitability and mechanical hypersensitivity. Phospholipase A2, tumor necrosis factor α, metalloproteinases and some other substances were found in great quantities in the degenerated nucleus pulposus. These were found able to cause nerve root injury by partial demyelination that increases nerve root mecano-sensitivity making the nerve root more susceptible to mechanical pressure. The mechanical factor seems then to be able to trigger hyper excitability and the ectopic nerve impulses in primary afferent axons that cause neuropathic paresthesia and pain.

Ozone has the ability to influence both of the mechanical and biochemical sources of pain. The basic science studies on ozone activity, conducted in several university centers in Italy, found that the mixture of ozone and oxygen has a potent, dose-related, biological activity. At high concentrations (30–70µg O3/ml 02), it can cause alteration and destruction of tissue structures. At medium concentrations (20–30 µg O3/ml 02) it seems to affect the regulation of the immune system, while at low concentrations (~20 µg O3/ml 02) it improves the microcirculation.

Experimental studies indicate that at adequate concentration and volumes, ozone has no mutagenic properties. With respect to intradiscal injections, more than one biological effect of ozone seems to be involved. Ozone has the ability to influence both the mechanical and biochemical component of disc degeneration.

References
continued from page 69


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