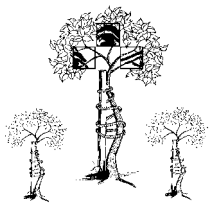
THE WORLDWIDE ORTHOPAEDIC MARKET – 2004-2005

Prepared by



KNOWLEDGE ENTERPRISES
The Ortho*People*

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THE WORLDWIDE ORTHOPAEDIC MARKET – 2004-2005

OVERVIEW OF THE MARKET

In 2004, revenues generated by sales of orthopaedic products worldwide neared $23 billion, an increase of 16 percent over 2003 global revenues. Every segment of the market experienced solid growth, with spine posting the most impressive increase, as noted in Exhibit 1.

EXHIBIT 1
2004 WORLDWIDE ORTHOPAEDIC PRODUCT SALES:
BY MARKET SEGMENT AND GEOGRAPHIC REGION
($BILLIONS)

Product Segment	*U.S.*	*Ex-U.S.*	*Total*	*Change vs. 2003*
Reconstructive Devices	$4.5	$4.2	$8.7	17.1%
Fracture Repair	$1.4	$1.3	$2.7	15.0%
Arthroscopy/Soft Tissue Repair	$1.3	$0.6	$1.9	12.7%
Spinal Implants/Instrumentation	$2.6	$1.1	$3.6	21.2%
Orthobiologics	$1.6	$0.5	$2.1	15.3%
Other Products	$2.6	$1.3	$4.0	9.5%
Total Market	**$14.0**	**$8.9**	**$22.9**	**15.5%**
Change vs. 2003	**15.5%**	**15.6%**	**15.5%**	

(Note: numbers may not add up due to rounding)

Products included in each segment:

Reconstructive Devices: hip, knee, shoulder, elbow, wrist, ankle and digit implants
Fracture Fixation: internal (plates, screws, intramedullary nails, pins, wires) fixation and external fixation products
Spinal Implants/Instrumentation: internal fixation devices and discectomy and vertebroplasty/kyphoplasty products
Arthroscopy/Soft Tissue Repair: scopes, cameras, instruments, soft tissue implants and repair kits
Orthobiologics: bone graft substitutes, allograft distribution/processing, autogenous bone and soft tissue replacement products, growth factors and viscoelastics
Other Products: power equipment, casting materials, soft goods, bracing systems, bone growth stimulators, cranio-maxillofacial fixation products, diagnostics, cement and cement mixing/delivery systems, infection control equipment, pulsed lavage/irrigation systems, continuous passive motion machines, image-guided surgery systems, etc.

For the first six months of 2005, sales growth remained robust in all areas; however, price pressures have begun to be felt by the larger reconstructive device companies in Japan and, most recently, in the U.S.

Worldwide, musculoskeletal conditions comprise the most frequent cause of disability and remain among the most costly illnesses to treat. All told, treatment of the more than 150 diseases and conditions within the musculoskeletal realm consume on average three percent of total gross domestic product in developed countries and cost the U.S. $254 billion in 2000, with developing countries incurring $100 billion in costs (nearly twice that of total foreign aid for these nations).

From arthritis to osteoporosis and fractures to dislocations, musculoskeletal conditions and diseases represent the primary non-psychological causes limiting activity in people of all ages worldwide. That is, those under the age of 18 are most likely to incur fractures and sprains, while the elderly (mostly women over the age of 50) are most likely to suffer from osteoporosis. Arthritis afflicts more than 500 million people, 69 percent of whom are under the age of 65, and the vast majority (90 percent) of people over the age of 30 will have back problems at some point in their lives.

Today, bone and joint diseases account for half of all chronic conditions in people over 50 years of age in developed countries. With the predicted doubling of the number of people in this age group by 2020 and the widespread incidence of musculoskeletal conditions in all age groups and in all parts of the world, demographics alone will drive growth in the global orthopaedic marketplace. Improved access to healthcare and improved standards of living in emerging economies should also contribute to solid growth in orthopaedic procedures into the future. Of note, although the U.S. accounts for more than 60 percent of the global orthopaedic marketplace, it is peopled with just five percent of the world's population. A similar dynamic emerges with Europe and Japan, the second and third largest orthopaedic markets. Clearly, then, opportunities exist for expansion of orthopaedic interventions in other parts of the world, particularly Asia and Latin America.

JOINT REPLACEMENT

Total global sales of joint replacement products (hips, knees, shoulders, elbows, wrists, digits) in 2004 approached $9 billion, an increase of just more than 17 percent over 2003 sales. Growth from 2003 to 2004 slowed from the prior year's rate of nearly 20 percent, largely due to smaller contributions of price and mix to overall growth in the U.S. market.

As has been the case historically, the world's five largest joint replacement companies – **Zimmer, Johnson & Johnson** (JNJ), **Stryker**, **Biomet and Smith & Nephew** (SNN) – controlled the vast majority – 87 percent – of hip, knee, shoulder and other joint product sales in 2004.

Companies with sales of less than $200 million that sell joint replacement products number more than 100. Many focus primarily on particular geographic regions (e.g. **Encore, Exactech and Hayes Medical** in the U.S.; **Japan Medical Materials and Japan MDM/(Ortho Development)** in Japan; **United Orthopedic** and **Tianjin Taishan Medical** in Taiwan and China, respectively; **Aesculap**, **JRI**, **Lima**, **Mathys**, **Tornier** and **Waldemar Link** in Europe; **Baumer, Implantes Fico and Ortosintese** in South America; **Protetim** in Eastern Europe; **Roth Medical** in South Africa; **Sushrut** and **Uma Surgicals** in India. Others have introduced niche products that either address particular surgeon philosophies (e.g. **Apex** and **Portland** in modular implants, Link and **Stanmore** in salvage/revision implants, **Symbios** in customs) or particular subspecialties (e.g. **Ascension**, **Bioprofile** and **Kinetikos Medical**/KMI in small joints).

In 2004, the number of joint replacement procedures performed worldwide exceeded two million, with most performed on people suffering from arthritis. Worldwide, more than 190 million people suffer from osteoarthritis (OA), the predominant diagnosis leading to joint replacement.

Eighty percent of people with OA report some form of limitation in movement or activities, and knee OA has been found to be as disabling as any cardiovascular disease (except stroke). Estimates indicate that 40 percent of people over the age of 70 suffer from OA of the knee and OA accounts for the primary diagnosis underlying the need for hip and knee replacement. Since the majority of hip and knee replacement procedures are performed on people over the age of 65, as the world's elderly population increases (at a

rate three times faster than that for the population overall), volumes of joint replacement procedures should increase as well. Growth in joint replacement will come, as well, through geographic expansion and application of technologies to a younger patient heretofore "gatekept" from joint replacement.

For instance, many of the world's less-developed countries (in terms of healthcare) do not now provide advanced orthopaedic care. In China alone, just 20 percent of orthopaedic surgeons perform many joint replacement procedures, most only performing hip replacement. Of note, orthopaedic surgeons in China reportedly perform fewer knee replacement procedures than U.S. surgeons perform ankle replacements. With more than 100 million Chinese people suffering from arthritis, China remains a substantial untapped market for joint replacement. Similar demographics hold promise throughout the Pacific Rim, and numerous local manufacturers have established businesses to serve these markets, as evidenced by the strong presence of United Orthopedic in Taiwan and **Kanghui** in China.

In 2004, hip and knee implants accounted for $4 billion and $4.2 billion in global revenues, respectively. The remainder of the market's value derived from the sale of shoulder implants ($300 million) and other joints. While the world's largest joint replacement companies generate the vast majority of their reconstructive revenues from hip and knee implant sales, all also offer shoulder implants, with **DePuy** the market leader in this segment. DePuy, Stryker, Biomet and Zimmer also market elbows, DePuy and Biomet sell wrist implants and DePuy, **Wright Medical** (WMGI) and Zimmer market finger implants, the latter outside the U.S. only.

Among smaller companies, Tornier has built a solid shoulder franchise, with elbow products gaining traction, as well. Ascension markets FDA-cleared and CE Mark approved silicone and pyrocarbon digit implants along with the first pyrocarbon TMC implant and the first pyrocarbon hemi-arthroplasty device to receive FDA market clearance (for treatment of thumb-based arthritis). Bioprofile markets its pyrocarbon carpal and radial head implants outside the U.S., while **Small Bone Innovations'** products (ulnar and radial head replacements and digits) and those offered by **Nexa Orthopedics** (biosilicon elastomeric toe implants) find their primary audience among U.S. orthopaedic surgeons. In ankle replacement, only DePuy currently markets an FDA-cleared total ankle system in the U.S., although Endotec and Link both have mobile bearing ankle implants in the FDA queue. Baumer, **Corin**, **Eska**, **Euros**, **FH Orthopedics**,

Integra LifeSciences, Japan Medical Materials, Link, Protetim, **Sovereign Medical** and Tornier sell their ankle systems outside the U.S.

From **Orthosonics** with its ceramic metatarsophalangeal implant to **Aptis Medical**, with its CE Mark approved and FDA cleared distal radioulnar joint, joint replacement worldwide encompasses a wide variety of companies in all corners of the globe. Most market traditional implants although novelty can be found in the likes of companies like **Disc-O-Tech**, with its Fixion hip system, which incorporates a reduced diameter stem that is expanded within the femoral canal with saline.

A comprehensive list of companies with reconstructive device franchises can be found in Exhibit App-1 in the Appendices at the end of this overview.

Although most hip and knee replacement procedures today are performed on people over the age of 65, over the past few years, in the U.S. at least, a trend has emerged with younger patients undergoing joint replacement procedures. In 1997, Baby Boomers (those aged 38 to 56) comprised 16 percent of hip replacement and 12 percent of knee replacement procedures performed in the U.S. Within four years, they accounted for 21 percent and 15 percent of hip and knee replacement procedures, respectively. Furthermore, in the U.S. in 1990, the Federal government's Medicare program paid for 66 percent of total hip and 71 percent of total knee cases. By 2003, Medicare's contribution had fallen to 59 percent of total hip and 61 percent of total knee. In Canada, a shift to a younger population for joint replacement has been more pronounced. For instance, the number of knee replacement procedures performed in those under the age of 55 rose 90 percent over a seven year period compared to a 51 percent increase in procedures overall.

This movement towards a younger patient comes largely as a result of technologies and procedures more amenable and applicable to treatment of a younger population. Certain patient characteristics contribute, as well. That is, OA, the primary indicator for joint replacement, results from normal wear and tear of the joints. However, injuries also contribute to its incidence and a more active population will likely spur increases in the incidence of arthritis in a younger population. Finally, obesity has been identified as a contributor to increases in arthritis (and meniscal tears and back problems) and, interestingly enough, from

1999 to 2003, the proportion of obese people undergoing joint replacement in the U.S. outpaced procedure growth by nearly two-fold. With obesity worldwide at "epidemic" proportions according to the World Health Organization, it, too, may serve to propel joint replacement procedure volumes.

One of the primary culprits leading to failure of joint replacement implants is polyethylene, which has been shown to wear and cause osteolysis or bone death and subsequent implant failure. In the past, orthopaedic surgeons delayed joint replacement in their younger patients due to concerns over wear of certain implant components. However, the introduction (in the U.S.) and increased penetration worldwide of alternative bearing materials has had a significant impact on broadening the base of joint replacement to a younger population. Metal-on-metal (MoM) and ceramic-on-ceramic (CoC) hip components do not incorporate polyethylene in their designs and, thus, may provide an alternative for treatment of younger patients. Most companies market MoM outside the U.S., with Biomet, DePuy, Encore, WMGI and Zimmer offering systems in the U.S.

While Encore, Stryker and Wright dominated the U.S. market for CoC systems from 2002 to 2004, by the end of September 2005, Biomet, DePuy and Smith & Nephew had also received clearance for CoC hip systems in the U.S., with ceramics sourced from **CeramTec**. Within their first three years on the market, CoC hip systems comprised more than 30 percent of hip sales for Stryker and Wright. Zimmer remains the sole large reconstructive device company without a CoC offering in the U.S., although the company has marketed CoC systems for several years outside the U.S. and expects to gain entry to the U.S. market by year's end. Of note, in Japan and Europe, ceramic bearing surfaces find application not only in femoral heads and acetabular cup liners, but in shoulder, knee, elbow and ankle articulating surfaces, as well.

While CeramTec and Japanese companies provide much of the ceramic technology used in joint replacement products, **Amedica** believes it has developed materials with improved wear characteristics based on its proprietary, high-strength, high toughness, biocompatible ceramics. The company is developing not only ceramic femoral heads (which most companies already distribute), but has also patented metal-on-ceramic bearings that could be used in hip and knee replacement. Amedica's technologies have application, as well, in bone graft and artificial disc applications.

Wright's A-CLASS Advanced Metal may also enhance wear of joint replacement products, while **Van Straten**'s ACCIS (Advanced Ceramic Coated Implant Systems) technology has already found use in hip and finger implants. Through ACCIS, a thin layer of titanium niobium nitride (ceramic) is applied to cobalt chrome implants, reportedly reducing wear by a factor of 40 compared to metal/poly and six to ten vs. standard MoM.

In addition to MoM and CoC materials, companies market "enhanced" polyethylene components for hip and knee replacement. Through radiation processes, the polyethylene undergoes a structural change (a.k.a. crosslinking) that more tightly bonds its molecules. The resultant material reportedly exhibits improved abrasion and wear characteristics, thereby extending its longevity.

"Enhanced" polyethylene has found its way into the majority of hip replacement procedures in which it could be used, with its usage in knees becoming more prevalent, as well. These "enhanced" polyethylenes carry a premium price and most of the leading manufacturers of joint replacement implants (except Exactech) market crosslinked poly.

In 2005, Biomet introduced its ArCom-XL Highly Crosslinked Polyethylene to the U.S. market, making it the first company in the U.S. to offer a second generation polyethylene. ArCom-XL reportedly demonstrated a 47 to 64 percent reduction in volumetric wear rate vs. Biomet's existing highly crosslinked poly. Stryker followed later in 2005 with clearance of its next generation X3 poly, a sequentially irradiated annealed poly for hip systems. X3 for knee systems could be introduced as well. Zimmer will work to commercialize CIMA (Cold Irradiated, Mechanically Annealed) highly crosslinked polyethylene, which may have application in higher demand situations.

In late 2005, Exactech received FDA clearance to market an enhanced polyethylene for acetabular liners. (The company had long remained reluctant to market a crosslinked poly due to concerns it has with the material's actual wear characteristics.) While an enhanced polyethylene will help Exactech compete in the U.S. market, the company has also entered preclinical testing on diamond-on-diamond (DoD) bearings, a technology developed by **Diamicron**. Exactech expects to be able to submit an Investigational Device Exemption (IDE) for the technology in 2006 with clinical implantations beginning outside the U.S. as

well. Exactech is not alone with the DoD technology, however, as Biomet obtained semi-exclusive worldwide rights to market joint replacement products developed from Diamicron's polycrystalline-diamond compact technology, which holds promise in improving wear.

Oxinium, an oxidized zirconium manufactured and marketed by Smith & Nephew, also has exhibited superior wear properties. Through the first half of 2005, Oxinium usage accounted for 40 percent of the company's U.S. knee implants and more than 40 percent of U.S. hip implants that could take Oxinium. Although predominantly sold in the U.S., Oxinium is also available in Australia, Canada and Europe.

Tecomet has developed Tecotex, computer-generated, etched 3D implant surface textures with undercut edges that potentially enhance fit, stability and longevity of implants. Tecomet can create surfaces of any configuration and complexity including acetabular cups, implant stems, knee components and spinal cages and has, thus far, textured pure titanium, titanium alloy and different types of stainless steels.

While alternative materials may help mitigate implant wear in younger, more active patient populations, a variety of less "traditional" joint replacement products – surface replacement, mobile bearing knees, unicompartmental knees, etc. – also provide options for patients whose disease process may not warrant total hip or knee replacement.

With a surface replacement hip, the surgeon removes only the surface of the femoral head, replacing it with a hemispherical implant that fits within the acetabular shell. Because a minimal amount of bone is resected, surface replacement surgery is far more conservative and thus, may be more appealing to a younger patient.

In September 2005, the Orthopaedic and Rehabilitation Devices panel of FDA recommended for approval of SNN's Birmingham MoM resurfacing hip (BHR) (manufactured by **Finsbury Orthopaedics**). The BHR has been used in more than 33,000 procedures outside the U.S. SNN acquired the technology through its 2004 purchase of **Midland Medical Technologies**.

Data in Smith & Nephew's submission to FDA for the BHR derived from one clinician outside the U.S. If cleared by FDA based on this data, the BHR would become the first device since the 1980s to receive clearance in the U.S. based solely on ex-U.S. data and that from a single clinician.

Wright Medical and Corin both have submitted Premarket Approval Applications (PMAs) to FDA for their Conserve Plus and Cormet MoM resurfacing hips, respectively. In 2005, Stryker signed an agreement with Corin for exclusive ten-year U.S. marketing and distribution rights to the Cormet.

DePuy launched its Articular Surface Replacement less invasive hip outside the U.S. in 2004 and expects to file an IDE for the product in the U.S., as does Zimmer with its Durom and Biomet with the ReCap Total Resurfacing System. In Europe, Biomet, Finsbury, Smith & Nephew, Van Straten and Zimmer market their respective resurfacing hip products, with **Global Orthopaedic Technology** concentrating on the Australian market with its ICON hip resurfacing, a "next" generation BHR.

Estimates place the penetration of resurfacing hips at ten to 15 percent of hip units sold in the U.K. and as much as 30 percent of those sold in Australia.

More conservative still in the joint replacement arena is **Arthrosurface**'s HemiCAP (Contoured Articular Prostheses) line of products for replacement of damaged, irreparable articular cartilage in hip, shoulder, knee and toe. The company received CE Mark approval for distribution of the HemiCAP devices for all indications, while FDA clearance has been obtained for hip, shoulder and toe. Arthrosurface is conducting U.S. clinical trials for the HemiCAP for repair of lesions on the femoral condyles of the knee. More than 200 HemiCAP knees, hips, shoulders and great toes have been implanted in the U.S., Europe and Australia.

Salubria obtained CE Mark approval and clearance in Canada for its SaluCartilage in treatment of cartilage damage, as a meniscal implant and as an interpositional spacer. The technology centers on a soft, compliant biostable hydrogel that contains water in similar proportions to human tissue. Since its European regulatory clearance in 2002, the product has been used in several countries in the European Union

to treat articular cartilage defects in the knee, foot, and shoulder. Preparation of the FDA submission required for sale in the U.S. is ongoing.

Impliant has been developing polyurethane implants since 1999 and received CE Mark approval for its Cushion-Bearing Femoral Head in 2004. The product comprises a metal core with an elastomeric covering for articulation against cartilage.

ConforMIS received a 510(k) (as **Imaging Therapeutics**) for its Interpositional Knee Mini-Repair System, a custom cobalt chrome implant based on a patient's magnetic resonance scans. Implanted through minimally invasive techniques, the device serves as a non-fixed, intra-articular support for treatment of degeneration in one compartment of the knee. From mid-2004 to early 2005, approximately 30 of these procedures had been performed in Germany, Hong Kong, Korea and the U.S. ConforMIS received FDA clearance in early 2005 for an MIS (minimally invasive surgery) unicompartmental knee system based on patient CT scans.

Although Zimmer's acquisition of **Centerpulse** gave it a unicondylar interpositional implant, the company has done little with the UniSpacer technology.

Mobile bearing knees (MBKs), designed to reduce contact stress and subsequent potential wear of the polyethylene, also address wear issues in knee replacement (and some ankle replacements) and may find more application in a younger, more active patient population. While most manufacturers market MBKs outside the U.S. (and have for decades), DePuy remains the only company in the U.S. with an FDA-cleared MBK. During 2004, FDA reviewed downclassification of MBKs in the U.S. and a disposition by the agency was expected in 2005. In response to potential downclassification, Corin ceased enrollment in its U.S. clinical trials for its mobile bearing Rotaglide+ knee. However, as of the end of the third quarter of 2005, FDA had not yet disposed on downclassification, thereby leaving DePuy to monopolize the largest market for mobile bearing knees.

The rapid introduction and extensive marketing of more conservative, less invasive technologies will also contribute to growth in joint replacement moving forward. Unicompartmental knees (unis), for instance,

address OA in a single compartment of the knee and their use in the U.S. has quadrupled since 1999, with most of the largest companies marketing unis on a worldwide basis. Biomet's clearance for its Oxford Unicompartmental Knee System in the U.S. in 2004 marked the first clearance for a "free-floating" meniscal device in the U.S. The company sells other uni systems outside the U.S., as do all key joint replacement companies as well as smaller, more regionally based competitors.

Patellofemoral joint (PFJ) replacement offers respite for those patients with arthritis affecting the patellofemoral compartment of their knees. Primarily used outside the U.S. and available from companies as varied as **Ceraver Osteal** and Zimmer, clearance for PFJs in the U.S. has been granted to Biomet, **Kinamed**, Smith & Nephew (in mid-2005), Stryker and Zimmer.

While the market for primary joint replacement should increase at a healthy rate over the next few years, a significant market also exists for revisions, which now account for more than ten percent of some companies' total joint replacement sales. Stanmore and Waldemar Link have long distinguished themselves for their revision and salvage implant lines, and most reconstructive device companies have worked to expand their franchises in these areas simply to address additional surgeon and patient needs. Of smaller players, **Portland Orthopaedics** and **Apex Surgical** (acquired by **OMNI Life Science** in 2005) focus on modular hip implant systems with key application in revisions.

Bone cement (typically polymethylmethacrylate or PMMA) finds use in serving as a grout to "fix" joint replacement implants into place and in shoring up vertebral fractures. Approximately half of hip stems and acetabular components and most knee tibial components are cemented into place (in the U.S., cementless hip systems claim 60 percent or more of units sold). All major implant manufacturers market cement products for joint replacement applications, including cement mixers, bowls, guns/injectors (for introducing the cement) and bone cement. Stryker has long claimed the lion's share of the market worldwide, a position it strengthened in 2003 when FDA cleared its Simplex P bone cement with tobramycin, marking the first such clearance in the U.S. for an antibiotic-laden bone cement. Of note, for more than 20 years, surgeons outside the U.S. have used antibiotic bone cements (approved for marketing by orthopaedic companies) when performing revision joint replacement surgeries.

Stryker cleared the way for other antibiotic bone cements to enter the U.S. market and, to date, Biomet, DePuy, Exactech and SNN have been granted clearances in the U.S. for antibiotic bone cements for use in revision joint replacement. In addition, Exactech has made great revenue advances in its cement business through the sale of its InterSpace implants. The devices, which are preformed antibiotic-laden knee implants, find application as temporary implants between stages in patients undergoing two-stage revision for infected total knee replacement. Exactech introduced the products in mid-2004 as a result of its exclusive distribution agreement with **Tecres**, which markets a full line of bone cements and antibiotic-loaded temporary implants outside the U.S. In mid-2005, Biomet received clearance from FDA to market its StageOne Disposable Spacer Molds for knee revision, the first company to receive such a clearance. StageOne comprises a series of silicone molds for use following infection, in place of previously available hand-made bone cement spacers. The company sells cement spacers outside the U.S. as well. DePuy also sells temporary cement implants under the Prostalac brand name; however, unlike the off-the-shelf Exactech implants, the Prostalac devices must be custom fabricated for each specific patient.

Among the leading joint replacement companies, Zimmer's market share in bone cement has lagged behind the company's share in joint replacement. In mid-2005, Zimmer sought to remedy this situation and acquired the U.S. distribution rights for Palacos bone cement products manufactured by **Heraeus Kulzer**. Zimmer will assume an exclusive position in the U.S. in 2006. The agreement with Heraeus gives Zimmer not only standard bone cements, but also FDA-cleared Palacos RG with Gentamicin antibiotic, which has been marketed in Europe for more than 30 years.

This new Zimmer relationship follows Biomet's commitment to reduce its dependence on external suppliers of bone cement, including Heraeus. In early 2005, Biomet noted that it would begin its own internal development and manufacture of Cobalt bone cement, with Heraeus continuing to supply the company with cements through the end of 2005. Biomet's Cobalt cement, specifically designed for use in MIS applications, will be available with and without antibiotic.

A change in bone cement relationships also impacted **aap Implantate**, which received a termination notice from its supplier of Palacos in early 2005. aap had been the exclusive distributor of Palacos in Germany. In mid-2005, it signed on as **Biomet Deutschland**'s bone cement sales partner.

Of smaller companies, **Advanced Biomaterial Systems** (ABS), Baumer, **Bidoia**, Ceraver, Corin, **Gruppo Bioimpianti**, Lima and **Summit Medical** also market bone cements and accessories for joint replacement applications in various geographic regions.

When faced with revision of cemented implants, a number of handheld and power instruments are available to the surgeon for removal of the cement. Non-manual systems specifically designed for revision of cemented and cementless joint replacement components have been developed by various companies, from Biomet to **Electro Medical Systems**. Endoscopic removal of components through ultrasonic means is available through the Orthosonics' (**Orthofix**) OSCAR system, which uses vibrating waves to soften bone cement for easier differentiation from bone and removal from within the bone canal. Biomet's Ultra-Drive system also uses ultrasound, but can be used to remove both cemented and cementless implants. So, too, can the pneumatically-driven Swiss OrthoClast from Electro Medical Systems, Exactech's Acudriver and **Saturn Orthopedics'** Accu-Jack automated osteotome system.

Of all the trends in joint replacement, MIS technologies have received the most attention from patients, hospitals and Wall Street. In orthopaedics, MIS initiatives typically center on the refinement of joint replacement instruments such that they can be used with standard implants without compromise to surrounding structures. MIS techniques allow for smaller incisions (e.g. two to five inches vs. standard eight or more inches), minimal disruption of key soft tissue integrity (e.g. quad-sparing in the knee) and reportedly more rapid rehabilitation. Through the first half of 2005, more than 4,000 surgeons and other hospital personnel had been trained on MIS techniques for hip and knee replacement and more than 6,000 instrument sets had been "installed" worldwide through Aesculap, Biomet, DePuy, Exactech, Smith & Nephew, Stryker, Wright Medical and Zimmer. While the MIS "phenomenon" has been predominantly targeted at the U.S. patient, the larger joint replacement companies have expanded their reach into Europe, where Waldemar Link has introduced specific MIS instruments for use with primary total hip and unicondylar knee products and **Medacta** markets specific MIS implants, instruments and ancillary equipment for hip replacement.

Most existing MIS systems use standard implants; however, all of the larger joint replacement companies are developing and commercializing implants specifically designed for MIS applications. Those cleared

in the U.S. include Zimmer's NexGen MIS Tibial Component, which can be assembled within the patient, and modular hip components from Biomet and Wright.

All across the spectrum of products and technologies, joint replacement worldwide should continue to post solid growth. A more involved, educated and proactive patient will demand less invasive, less traumatic surgery, potentially expanding the pool of patients undergoing some form of joint replacement procedure. Orthopaedic surgeons, who may have withheld joint replacement in a more active group two years ago, now have a full array of options for treating patients all along the continuum from early disease to revision. At the same time, an elderly population will continue to undergo wear and tear that are a natural part of the aging process. All told, joint replacement procedure volumes should increase in the high single digit range for the next five years, with knee procedure growth outpacing that for hips.

However, in the U.S., which accounts for more than half of all dollars spent on joint replacement, price increases have slowed from four to five percent a few years ago to one to two percent in 2005. In addition, with penetration of enhanced polyethylene and cementless hip stems exceeding 60 percent and CoC and MoM at their peak of penetration, as well, the shift from less expensive to more expensive products has slowed substantially. As a result, growth in the overall joint replacement market is expected to slow in the near term. U.S. hospitals continue to push back on premium-priced technologies and some have begun to negotiate more substantial discounts on joint replacement products. Furthermore, at least one major hospital group in the U.S. has proposed implementing gain sharing within its orthopaedic business unit. Through gainsharing, surgeons share in savings incurred through their use of less expensive implants. Proponents of gainsharing are attempting to introduce legislation to allow for a pilot gainsharing project in ten states.

While price pressures will likely not abate in the U.S. and should remain in place outside the U.S., an estimated ten million people in the U.S. who suffer chronic joint symptoms are not getting the treatment they could. Orthopaedic manufacturers are fully aware of the potential that exists for expanding the pool of joint replacement patients, not only those who don't seek help but also those who are unwilling to wait in pain until they are "old enough" for joint replacement. In addition, waiting lists for joint replacement in Canada and parts of Europe have compelled some patients to seek care in other parts of the world, often at

premium prices to what they would have paid in their own countries. Finally, direct-to-consumer (DTC) marketing efforts on the part of most major orthopaedic companies have skyrocketed over the past three years, reaching not just print, radio and Internet media, but national television, as well. Biomet, DePuy and Stryker have all advertised on U.S. television during "prime time" viewership hours.

While DTC and demographics will further drive procedure growth, market growth will slow due to price pressure and some mix shift away from more expensive technologies in the U.S.

FRACTURE FIXATION

Sales of products used in the repair of fractures reached $2.7 billion in 2004, an increase of 15 percent over 2003 sales. Traditional fracture repair centers on the use of internal fixation (e.g. plates, screws, pins, wires, intramedullary nails, etc.) and external fixation devices marketed by more than 100 companies globally. The five largest companies in the global fracture fixation marketplace – **Synthes**, Stryker, SNN, Zimmer and JNJ – control 77 percent of the market, with additional solid positions in the market claimed by companies like **Acumed**, Aesculap, Biomet, **Hand Innovations**, Orthofix and **Osteomed**. Aside from these larger companies, the fracture repair market remains highly fragmented, with hundreds of companies manufacturing and distributing competitive products throughout the world.

A comprehensive list of fracture repair companies and the products they market can be found in Exhibit App-2 in the Appendices at the end of this overview.

A fracture requiring orthopaedic services occurs approximately every 14 seconds in the U.S., and half of all Americans will fracture a bone and receive treatment for it prior to their 65th birthday. Fractures account for approximately 15 percent of all musculoskeletal injuries in the U.S., with costs for hospital care, office visits and days missed from work (including lost wages) approaching $13 billion annually. Fractures number more than 50 million worldwide and most result from accidents, falls and activity-related injuries. Interestingly, urbanization of many countries could bring with it an increase in fracture incidence. For instance, in areas long traversed by bicycle, the introduction of automobiles has contributed to road accidents and an increase in fractures.

While most fractures afflict people under the age of 65, osteoporosis affects an older population, leading to more than three million hip, vertebral, forearm and other fractures each year. In fact, according to statistics, osteoporosis causes one spine fracture every 45 seconds. More than half of all people 50 years of age and older have low bone mass, putting them at risk of developing osteoporosis and related fractures. Treatment of osteoporosis fractures could exceed $60 billion worldwide by 2030.

More than 40 percent of all women and 20 percent of men will have at least one osteoporosis-related spinal fracture before they are 80 years old. Furthermore, half of all women and one in eight men over the age of 50 will incur an osteoporosis-related fracture in their lifetime.

Certainly an aging population will spur growth in the treatment of osteoporosis-related fractures. Expanded access to healthcare in underdeveloped regions will also contribute to steady growth in the fracture fixation market over the next decade. For instance, by the year 2050, more than half of all hip fractures will take place among the Asian population, many of whom have no access to adequate care for their conditions. With an estimated 450 million Asian women over the age of 65 slated to develop osteoporosis, today's three million osteoporotic fractures could increase substantially.

In 2004, more than six million fracture repair procedures were performed globally, most often on the radius/ulna, wrist/hand, tibia/fibula and ankle/foot. Demographics will play a key role in the steady growth expected in the fracture fixation market into the future, largely in the area of osteoporotic fracture repair.

Vertebroplasty/Kyphoplasty

Today, treatment of osteoporotic spine fractures consists primarily of conservative, non-operative modalities. However, over the past five years, volumes of vertebroplasty and kyphoplasty procedures used to treat vertebral fractures have increased by more than 30 percent per year.

Numerous orthopaedic and general medical companies – **ArthroCare** (internally and through its acquisition of **Parallax**), Biomet (through its acquisition of **Interpore International**), **Cook Medical**, Disc-O-Tech (outside the U.S.), Integra LifeSciences (through its purchase of **Spinal Specialties**), **Jupiter Surgical**, **Medtronic Sofamor Danek** (MSD), **Spineology**, **Spine Wave**, Stryker, Synthes – have developed

products that facilitate the percutaneous introduction of some sort of biomaterial to shore up and stabilize vertebral compression fractures. **Kyphon**'s technology, sold predominantly in the U.S., centers on balloon-based kyphoplasty, which creates a cavity into which bone replacement materials can be introduced. The company extended its intellectual property position during 2005 with the licensing of a portfolio of patents relating to the creation of voids in or the moving of tissue/bone for most orthopaedic applications, including those in the spine.

As part of its expansion outside the U.S., Kyphon received approval to enroll patients in a kyphoplasty clinical trial in Japan in 2005. The company estimates that 500,000 new vertebral compression fractures due to osteoporosis occur each year in Japan.

The Disc-O-Tech SKy Bone Expander System offers a similar technology – a polymeric device that is inserted into the vertebra and then expanded. Once optimal vertebral height has been attained, the device is removed and void filler is introduced into the cavity. In mid-2005, Disc-O-Tech was barred by a U.S. court from importing or selling its SKy Bone Expander in the U.S. due to a patent infringement suit brought by Kyphon. Later in 2005, the company introduced its B-Twin Expandable Spinal Fusion System (ESFS) to U.S. spine surgeon, seeking participants for a possible U.S. pivotal study of the device. The CE Mark approved B-Twin ESFS, used in more than 9,000 procedures in Europe, allows for MIS introduction of a titanium implant that is expanded in situ.

A novel approach to building up weakened osteoporotic vertebra comes through Spine Wave's StaXx Fracture Repair System. StaXx comprises the percutaneous injection of interlocking wafers into the vertebral body, allowing the surgeon to build a structural, height restoring implant. The CE Mark approved system can be used with standard bone void fillers employed in vertebroplasty applications.

ArthroCare's Coblation technology has also found application in the creation of voids in the spine and can be used prior to percutaneous cement injection. Stryker offers a complete line of products for percutaneous cement delivery. **Medtronic**'s (MDT) Equestra Fluid Delivery system provides surgeons with a method for injection of bone cement into a surgical site, while Synthes' cavity creation device reportedly

relies on mechanical methods for addressing void filling applications. Neither Medtronic nor Synthes has introduced its products on a widespread basis.

Spineology's OptiMesh bone graft containment and reinforcement system received CE Mark approval and FDA clearance for use in treatment of vertebral body defects. OptiMesh features proprietary technologies that conform to defect structures and may minimize the potential for materials to migrate from the site of application.

Remaining true to its core strengths, Cook focuses on biomaterial delivery instruments, while Jupiter distributes a low-pressure substance delivery system in the U.S.

Companies marketing bone cements and accessories for use in vertebroplasty/kyphoplasty procedures include ABS (Concert Spine VR radiopaque bone cement, designed for use with the Plexis mixing and delivery system), ArthroCare (Parallax Acrylic Resin), **Bone Support** (SpineSupport), **Cardinal Health** (Ava-Tex Radiopaque Bone Cement with specially-designed mixing kit), Kyphon (Kyphx Hv-R), **Showa Ika** (VP Needle transpedicular injection device), Stryker (SpinePlex and cement delivery systems), Tecres (Mendec Spine Kit) and **Teknimed** (Spine Fix biomimetic cement for vertebroplasty).

Bio-Medical Devices offers its Intelleject for delivery of viscous materials, while Bone Support's Cerament system features delivery devices for injection of the company's bioceramics. (See Orthobiologics.)

Although PMMA bone cement remains the predominant material used in vertebroplasty procedures, other biomaterials for vertebral compression fracture repair have either been introduced outside the U.S. and/or entered clinicals in the U.S. Injectable materials and delivery systems also have application in the treatment of Colles' fractures and in screw augmentation (both also often related to osteoporosis). A review of biomaterials used in orthopaedic applications can be found in the Orthobiologics section of this overview.

Bone Growth Stimulation

While vertebroplasty primarily addresses weakened or osteoporotic bone, bone growth stimulation finds key usage in the treatment of the estimated five percent of fractures that do not heal properly (and as an adjunct to spinal fusion). Global revenues for bone growth stimulation for all applications neared $400 million in 2004.

Stimulation is spurred through various technologies (e.g. ultrasound, pulsed electromagnetic fields, etc.), all of which have demonstrated their ability to induce the growth of bone. Biomet's **EBI** subsidiary, **dj Orthopedics** (through its acquisition of **OrthoLogic**'s bone growth stimulation business), Orthofix and Smith & Nephew all sell bone growth stimulators for fracture or spinal applications. Although more than 90 percent of bone growth stimulation sales occur in the U.S., U.S.-based companies are looking outside the U.S., where **Forward Medical Technology** concentrates sales of its stimulator business. In mid-2005, Orthofix received regulatory reimbursement clearance in France to market its Physio-Stim for treatment of pseudarthrosis and delayed union and will seek similar clearances in other European countries. dj's U.K. subsidiary launched both of its stimulators in early 2005, while the first of its bone stimulation units entered clinical trials in Germany. dj will evaluate the opportunity for its products in Japan, as well.

One of the more important events in bone growth stimulation came with Orthofix's clearance to market its non-invasive, low-level pulsed electromagnetic field Cervical-Stim bone growth stimulator for use as an adjunct to cervical spine fusion in high-risk patients. Orthofix may also seek clearance of the device in non-operative salvage applications as a follow-up to unsuccessful cervical fusion. Most companies' spinal bone growth stimulators have been cleared for use in lumbar applications only. dj will meet with FDA to determine the protocol required for submitting for approval of cervical stimulator applications for its devices.

Another key event in stimulation came with expanded Medicare coverage of Smith & Nephew's Exogen Bone Healing System used to treat nonunion fractures. In 2000, the low-intensity pulsed ultrasound device was cleared for use in treatment of nonunion fractures only in those cases where prior surgery had failed to heal the fracture. The expanded coverage provides reimbursement for treatment of all nonunion

fractures, regardless of whether the fracture has had prior surgical intervention. Exogen is cleared, as well, for accelerating the healing of fresh fractures.

Extracorporeal shock wave therapy (ESWT) has long been used outside the U.S. for treatment of pseudarthrosis, delayed unions and nonunions, although no clearance for these indications has been granted in the U.S. Through ESWT, high-pressure shock waves are focused on a pathological treatment site, reportedly helping tissue and bone to heal.

While bone growth stimulators and, to a lesser extent, ESWT systems are used to spur bone to grow in nonunions or delayed unions, bone morphogenetic proteins (BMPs) have also been introduced to treat problematic fractures, with both MSD and Stryker receiving clearance to market BMPs for use in treatment of certain types of nonunion fractures in certain geographic regions of the world. See the Orthobiologics section for more information on their and other companies' products and initiatives.

Despite an intensely competitive fracture repair marketplace and the relative dominance of one company – Synthes – on a worldwide basis, newcomers continue to enter the space. Many newer entrants seek to emulate the success of Acumed, which has demonstrated that remaining focused (in its case on small bone repair) can create a viable, long-standing business. Hand Innovations created a niche segment for novel MIS distal radius repair products, causing most of the larger trauma companies (and some smaller ones) to follow suit. **Rigidfx** concentrates on fixation with its translucent, lightweight, low profile wrist fixator; **Triage Medical** with BoneLOK technology, which pulls fragments together using compression; **TriMed** with a minimally invasive distal radius wrist fixation system; and **Königsee**, whose fixed-angle plates serve numerous small bone applications. Within the past 18 months, **OrthoNetx** has established its niche in distraction osteogenesis for treatment of craniofacial deformities and limb length discrepancies, Newly-formed **DVO Extremity Solutions** launched an MIS dorsal intramedullary plate, with more extremity fixation and arthroplasty products in its development pipeline. **Merete** remains focused on novel fracture repair products – modular diaphyseal intramedullary spacer implants, small fragment locking plates and bone screws. Most of Merete's products are cleared for use in both Europe and the U.S. Finally, **Science for Bio Materials** (SBM) has developed Duosorb, a composite material of tricalcium

phosphate ceramic and Poly DL Lactic Acid. The company markets this resorbable technology for use with its locking plates and screws for high tibial osteotomy.

Interestingly, more strategic activities occurred in the area of small bone repair than any other space in orthopaedics in 2005. For instance, Integra acquired the small bone-focused **Newdeal** (fracture fixation and arthroplasty products); Nexa Orthopedics acquired **Futura Biomedical** and the StayFuse interphalangeal fusion product line from **Pioneer Surgical**; and Small Bone Innovations emerged through the combination of **Avanta Orthopaedics**, **Envision Manufacturing** and **Xtremi-T**, with licensing and distribution rights to **Artimplant**'s Artelon CMC-I Spacer and **Biorthex**'s Actipore porous titanium nickel alloy for small bone and joint applications. Zimmer broadened its trauma platform through worldwide distribution rights to a Universal Locking Plate technology. Zimmer's move appears to be a reaction to the highly-successful launch of Synthes' LCP (locking compression plate) products which, by mid-2005, had penetrated 60 percent of Synthes' U.S. business. The LCP products carry a substantial price premium and conversion from traditional to locking plates could serve to boost growth in the trauma market.

Based on the number of FDA clearances and new companies believing in the novelty of their fracture repair products, innovation is thriving in fracture repair. Demographically, with more than 6 billion people worldwide and two fractures per person per lifetime, the incidence of fractures likely will not slow over the next few decades. Couple these solid, healthy demographics with not only a more active population, but also increased industrialization and access to healthcare in certain parts of the world, and the future of fracture repair will remain a demographic gold mine. Steady growth should characterize this subsegment of the market for decades.

While stainless steel and titanium alloys have long been the materials of choice for fracture indications, resorbables have found a home in the segment, as well. Inion focuses on resorbables and markets resorbable mini plating system, pins, ankle fixation plates/screws and mesh (for containment of bone grafts and bone fragments). **Linvatec**, although primarily a sports medicine company, also sells resorbable nails, plates and screws, as do its sports medicine competitors, **Arthrex** and **Arthrotek**.

Other innovation in materials has come from **Tigran Technologies**, with its CE Mark approved titanium granules for bone replacement in fracture repair and/or as a scaffold for bone growth. The granules may also have application in implant coatings. Through its patented CFM (Composite Flow Moulding) process, **Icotec** can combine different fibers and matrices to create unique composites and has done so with fixation plates and translaminar pins. **Erothitan** has developed a unique a dynamic/flexible wire fracture "plate," while **InteliFUSE** has created staples through the use of shape memory alloys. The company's system includes StimuLINK shape memory alloy implants and the Warmsystem, a thermal device that recovers the StimuLINK's predetermined shape *in situ* allowing it to apply dynamic compression.

ARTHROSCOPY AND SOFT TISSUE REPAIR

Revenues from products used in more than 15 million open and arthroscopic soft tissue repair procedures in 2004 exceeded $1.9 billion, an increase of 13 percent over 2003 sales levels. Arthroscopes, cameras, fluid management systems, powered shavers and drills, manual instruments, radiofrequency systems and soft tissue repair implants (e.g. screws, anchors, tacks, etc.) comprise the products included in this segment of the market.

A comprehensive list of arthroscopy/soft tissue repair/sportsmed companies can be found in Exhibit App-3 in the Appendices at the end of this overview.

Smith & Nephew remains the market leader and it, in conjunction with the four other largest companies in the market segment (Stryker, JNJ, **ConMed** and Arthrex), captured 70 percent of global arthroscopy/soft tissue repair sales in 2004. Other key companies marketing arthroscopy/soft tissue repair products include ArthroCare, Arthrotek, **Karl Storz**, **Olympus** and **Richard Wolf**, with an additional 50 or more companies also competing in the marketplace, although on a significantly smaller scale or in particular niche areas (e.g. **Future Medical** in fluid management, **Inion** in resorbable fixation, **Ortheon** in tendon repair, Instratek in endoscopic soft tissue repair instruments, etc.).

Soft tissue injuries afflict people of all ages. An estimated 16 of every 1,000 people in the U.S. receive medical attention for sports-related injuries, the vast majority males. Sprains and strains most afflict peo-

ple under the age of 20, with most soft tissue conditions and diagnostic and surgical arthroscopy/soft tissue repair procedures occurring in those under the age of 65. As more people worldwide engage in physical activity, soft tissue injuries will increase concomitantly.

Although innovation in arthroscopy has been evolutionary over the past few years, improvements continue to emerge in visualization equipment (e.g. higher-quality digital cameras, systems for access to hard-to-reach areas, autoclavable cameras, flat screen monitors, etc.), diagnostic arthroscopy and thermal energy technologies.

In the area of diagnostic arthroscopy, in 2005, Arthrotek introduced its InnerVue diagnostic scope system for use in office and outpatient surgery settings. The system not only provides immediate diagnosis (obviating the need for the patient to go elsewhere for tests), but it also allows the surgeon to determine damage and appropriate treatment modalities. InnerVue is used primarily in knee and shoulder, with application in other small joints under investigation.

On the radiofrequency (RF) front, RF electrosurgical platforms use thermal energy to manipulate (e.g. remove, cut/sculpt, coagulate, shrink, etc.) soft tissue. A key indication for RF that has arisen over the past few years involves treating soft tissue instability, particularly in the shoulder. When collagen fibers are "heated," their molecular structure changes and they contract, leading to tighter joint spaces and purportedly more stable joints. ArthroCare, ConMed, **Mitek**, Smith & Nephew and Stryker dominate the RF subsegment of the market; however, unlike traditional electrosurgical systems, ArthroCare's Coblation technology employs lower temperatures, which may minimize thermal damage to the soft tissues. ArthroCare, too, has attained a solid patent position in the RF world, earning royalties on product sales from some of its leading competitors, some of whose products have been found to infringe ArthroCare patents. In mid-2005, the latest in ArthroCare patent infringement came to a close when the company signed a worldwide product supply agreement with **Smith & Nephew Endoscopy** through which it will manufacture bipolar and monopolar arthroscopy products for global sale by Smith & Nephew. A joint licensing agreement will also provide ArthroCare with royalty payments for all bipolar products sold by Smith & Nephew in the U.S. and for that company's bipolar shaver products manufactured and sold worldwide.

Waterjet technology has been used for many years in precision cutting. Both **Hydrocision** and **Erbe** have developed ultrahigh-pressure fluidjet technology systems for use in orthopaedic procedures. Erbe's system has application in percutaneous discectomy and synovectomy, while Hydrocision's systems have found a place in wound debridement (TraumaJet through Smith & Nephew), cutting, ablating and shaping soft tissue, and decorticating, removing and smoothing bone in arthroscopic procedures (ExoJet through Mitek) and, through Hydrocision for spine.

Lasers, too, have use in the removal and shrinkage of tissue in arthroscopic procedures. However, despite their having been on the market for decades, lasers have not made great inroads into the segment, largely due to their cost.

With respect to soft tissue repair technologies, biologics (See Orthobiologics.) continue to grow in popularity, as do resorbables. Arthrex, Arthrotek, ConMed, Mitek, Smith & Nephew and others market full lines of implants (resorbable and metal) for most soft tissue applications in all joints. Storz, Stryker and **U.S. Surgical** continue to build their soft tissue repair franchises, with Stryker often partnering with smaller companies that have expertise in soft tissue repair technologies.

For instance, Stryker serves as the exclusive North American distribution "partner" for Inion's sports medicine, craniomaxillofacial (CMF) and OTPS plate/screw/mesh system for treatment of small bone fractures or for supplementing long bone fixation. Inion focuses on resorbables and introduced the world's first colored resorbable anterior cruciate ligament (ACL) screw (the Hexalon) based on the company's resorbable Optima family of technologies. The Optima technologies blend rigid and elastic polymers (e.g. L-polylactic acid, D, L-polylactic, trimethylene carbonate and polyglycolic acid) for specific applications, from soft tissue repair to fracture fixation and bone graft containment. Inion has received clearance in Europe and the U.S. for the Hexalon device, as well as its Trinion Meniscus Screw for knee cartilage repair and Anchron Suture Anchor for use in orthopaedic and sports medicine applications, particularly those in the shoulder. Aesculap distributes the company's sports medicine products on an exclusive basis in Austria and Germany.

In 2005, faced with slower than anticipated sales by its distributors, Inion has begun discussions with new distributors for its sports medicine, dental and spinal products. Inion is also developing resorbable plating systems for spinal fusion/fracture repair and suture and tendon anchors for knee and shoulder reconstruction and will continue development of its OPTIMAPLUS technology that features small quantities of active compounds added to the polymer to promote healing.

Stryker Endoscopy also handles worldwide distribution of Biocomposites' Biosteon interference screw technology (calcium hydroxylapatite (HA) and poly-L-lactic acid (PLLA) for ACL/PCL reconstruction using bone-tendon-bone/semitendinosus tendon and allograft. ArthroCare distributes **Biocomposites**' line of resorbable composite screws including the BiLok ST (soft tissue) screw for ACL reconstruction and transverse fixation in femoral hamstrings, based on PLLA and calcium phosphate. Bilok was the first synthetic PLLA/calcium phosphate composite ACL interference screw to receive both CE Mark approval and FDA clearance.

With FDA clearance to market its Stratis ST ACL Reconstruction System and Femoral Fixation Implant granted in late 2004, **Scandius** launched the system in the U.S. in early 2005. The system provides tissue-to-bone tunnel compression and fixation at the joint line of the femur. Scandius focuses on arthroscopic ACL reconstruction, and plans to develop products for repair of articular cartilage, menisci and other soft tissue sports-related joint injuries. An infusion of cash in early 2005 will help the company expand its network worldwide and further its research and development initiatives.

Artimplant has worked for years to commercialize products based on developed numerous resorbable polyurethane scaffold technologies. In late 2004, the company received FDA clearance for the Artelon CMC-I Spacer for treatment of thumb base arthritis. Avanta (now part of Small Bone Innovations) distributes the Spacer (known as the TMC Spacer in Europe) outside of Scandinavia. Artimplant and Biomet signed a global development, license and supply agreement for a soft tissue repair implant product based on Artimplant's Artelon technology. The companies' first product under development is a tendon augmentation device which could be launched globally by the end of 2005.

Additional Artelon-based products have received CE Mark approval, including a bone scaffold, a membrane (e.g. soft tissue barrier, bone graft containment), an Augmentation Device ACL (first implanted in 1997) and a suture with application in tendon and ligament repair (also cleared in the U.S.). Future projects for Artimplant include development of Artelon for soft tissue reinforcement and as a bone void filler for orthopaedic applications.

Kensey Nash supplies a broad range of biomaterials-based sports medicine products for Arthrex. In addition, Kensey received FDA clearance to market its BioBlanket Surgical Mesh, manufactured from the company's proprietary resorbable collagen sheet technology. Initially cleared as a patch for soft tissue reinforcement and repair, FDA granted Kensey expanded indications for the Mesh specifically for the reinforcement of soft tissue in rotator cuff repair procedures. Kensey's orthopaedic development programs with the collagen technology include those targeting bone graft containment.

Invibio, a subsidiary of **Victrex**, is a leading manufacturer of polyetheretherketone (PEEK) plastics. The company provides PEEK-OPTIMA polymers to a wide range of orthopaedics companies throughout the world for such applications as finger implants, interbody fusion cages, hip stems, acetabular cup (as reinforcement) and, in sports medicine, as suture anchors, interference screws, washers, etc.

Other novelties in soft tissue repair have emerged through the efforts of **Axya Medical**, **Bonutti Technologies** and **Opus Medical** (now ArthroCare), all of which have commercialized technologies that obviate the need for knot tying during arthroscopic procedures. **KFx Medical** and **MedicineLodge** have also developed improved technologies for soft tissue repair.

Axya Medical introduced its AxyaWeld instrument for arthroscopic soft tissue repair in the late 1990s. The product incorporates the AxyaLoop, a suture loop that is secured with ultrasonic energy. In 2004, the company signed on ArthroCare for distribution of its bone anchors and select accessories and has since received clearance to market a resorbable bone anchor system. Axya will further develop wound closure technology and additional products for its Axya Shoulder Fixation System, which it claims is the only knotless fixation system capable of performing all shoulder repairs.

Bonutti's Unity Ultrasonic Fixation system utilizes an absorbable "fixation seat" that is loaded with suture and introduced endoscopically. Once the seat is in place, the suture is tensioned and the seat is ultrasonically welded to the suture. Through the technology, the surgeon need not tie knots.

The AutoCuff System from ArthroCare incorporates a suturing device with a knotless fixation implant for use in rotator cuff repair, Bankart repair and SLAP lesion procedures. With both CE Mark approval and FDA clearance, the AutoCuff system has found use in more than 20,000 rotator cuff repair procedures.

Following in the footsteps of Opus, KFx Medical hopes to further improve rotator cuff repair and is developing a minimally invasive technique for shoulder surgery in which the rotator cuff is secured to the bone using improved attachment techniques. Submission of materials to FDA could come in early 2006, with potential product launch in the second half of 2006.

MedicineLodge's ZipKnot suture fastener received clearance in the U.S. for approximation and/or ligation of soft tissues using sutures. The suture fastener obviates the need to knot tying outside the body and is deployed with a knot pusher. MedicineLodge seeks marketing/distribution partners for the product.

Ortheon Medical markets its Teno Fix system for the repair of severed or lacerated digital flexor tendons worldwide, with more than 1,000 procedures performed with the device in the U.S. since its FDA clearance in 2003. The TenoFix technology incorporates a stainless steel soft tissue anchor that attaches to the collagen fibers inside a tendon and supports significant load, thus allowing for active motion postoperatively and hence more rapid return to normal motion in the hand. Ortheon also markets the Teno Fix ACP, an arthroscopic suture cutter and knot pusher.

Synthetics used in repair/replacement of ligaments find a market primarily in Europe. Companies marketing synthetic ligaments include Corin (Ligament Augmentation and Reconstruction System for PCL, ACL, ankle and shoulder repairs), **Cousin Biotech** (intra- and extra-articular ligaments), **Ellis Development** (Nottingham Hood polyester soft tissue reinforcement device for rotator cuff repair), FH (Tenolig for Achilles tendon), **Fixano** (acromioclavicular ligament and Achilles tendon replacements), the **Neoligaments** division of **Xiros** (Leeds-Keio Connective Tissue Prosthesis for patellar ligament and quadriceps tendon repairs and the Leeds-Keio ACL), **Orthomed** (Ligastic polyethylene terephthalate for medial

collateral ligament reinforcement, acromioclavicular separation and trapeziectomy), **Surgicraft** (coracoclavicular ligament reconstruction, composite ACL ligament, other tendon/ligament augmentation), Teknimed (Achilles tendon reinforcement) and **Telos Medical** (synthetic ACL ligament).

To complement their lines, many arthroscopy and soft tissue repair companies also market postoperative pain pumps or other types of technologies for use in treatment of soft tissue pain. **Sgarlato** entered the pain pump market first with its portable pain control infusion pump, which releases analgesics continuously. **Advanced Infusion**, **Breg**/Orthofix, dj Orthopedics, **I-Flow, McKinley, Sorenson, Stryker Instruments** and Zimmer (through an agreement with **Baxter**) also sell pain pumps.

Pain management for soft tissue applications also comes in the form of ESWT. Companies and systems available outside the U.S. for use in treatment of chronic, painful soft tissue orthopaedic disorders like lateral epicondylitis, calcific tendonitis of the shoulder and plantar fasciitis include **Direx Medical** (Orthima), **Dornier** (Epos Ultra), **Medical Technologies & Services** (OrthoWave), **Medispec** (Orthospec), **Orthometrix** (Orbasone), **SanuWave** (OssaTron), **Siemens Medical Solutions** (Sonocur)**, Sonorex** (representing Siemens in certain countries) and **Storz Medical** (MiniLTH and Masterpuls). In the U.S., Dornier, Medispec and SanuWave market systems for plantar fasciitis, with ESWT systems from SanuWave and Siemens/Sonorex available, as well, for treating lateral epicondylitis. SanuWave acquired the orthopaedic ESWT business from **HealthTronics** in the fall of 2005 and will focus on non-urological shockwave therapies, while Orthometrix will pursue a PMA for the Orbasone device, which is manufactured by **Kimchuk**. Future indications for ESWT in the soft tissue arena may include treatment of supraspinatus tendon syndrome, medial epicondylitis, patellar tendonitis and achillodynis.

In prior years, consolidation in the sports medicine arena centered primarily on implantables. Activity over the past 18 months, however, has been most intense in the soft goods/bracing arena.

For instance, **Beiersdorf** and Smith & Nephew agreed to divest of their joint venture, **BSN Medical**, which focuses predominantly on casting, splinting, orthopaedic soft goods, fracture bracing, etc. dj Orthopedics led the way with strategic alliances, acquiring distribution rights to a new back bracing system,

acquiring assets for a stock and bill soft goods/rigid bracing business; and, finally, purchasing one of its Scandinavian distributors and the orthopaedic soft goods business of Encore Medical.

Ossür, which acquired Generation II in 2003, added **Royce Medical** to its portfolio of companies, expanding its orthopaedic bracing and supports business and **Tailwind Capital** purchased **Aircast**, best known for its ankle and walking braces. Amid all the positive momentum, **Bledsoe Brace** filed for Chapter 11 bankruptcy protection following the loss of a patent infringement case brought by Generation II Orthotics.

As in other areas of orthopaedics, biologics play a key role in soft tissue repair, most notably in rotator cuff repair technologies (e.g. Wright's GraftJacket, Biomet's CuffPatch, DePuy's Restore, Stryker's TissueMend and Zimmer's Permacol). These products and other biologically based soft tissue repair products (e.g. tissue-engineered cartilage, autologous cell transplantation, collagen/cartilage-based implants, scaffolds, stem cell technologies, etc.) are described in more detail in the Orthobiologics section of this report.

While orthobiologics will contribute greatly to growth in the arthroscopy/soft tissue repair market into the future, so too will increased activity levels and related sports injuries worldwide, introduction of procedure-specific technologies and improved resorbables and visualization systems. The use of computer-assisted surgery, too, will find an increased role in the repair of soft tissue injuries, with particular application in ACL repair.

SPINAL IMPLANTS AND INSTRUMENTATION

Worldwide, spine procedure volumes exceeded three million in 2004, including fusion, discectomy, disc replacement, vertebroplasty/kyphoplasty and fracture repair. Conditions related to back pain account for more hospitalizations than any other musculoskeletal condition and the back is the body part most often involved in work-related disabilities. In fact, low back pain caused more lost work days in the U.S. in those under the age of 45 than any ailment except the common cold and approximately one percent of the

U.S. population is chronically disabled because of back pain. In some parts of Europe, 80 percent of workers suffer from back pain.

Furthermore, 32 percent of people over the age of 18 are limited in their activity due to chronic back pain and, of 1,000 children, three of five will develop scoliosis severe enough to warrant surgical intervention. Costs to treat back conditions exceed $100 billion each year worldwide.

In 2004, sales of spinal implants and instrumentation (excluding biologics) topped $3.6 billion, up 21 percent over 2003 revenues. The robust growth in the spine market from 2003 to 2004 derived largely from expansion of the patient base for spine procedures; increased use of spinal instrumentation in spinal fusion procedures; increased volume of 360s, procedures that utilize both anterior and posterior instrumentation for support; expansion of vertebroplasty/kyphoplasty procedures; increased application of MIS systems for treatment of back problems; etc. These same factors will contribute to growth into the future, as will the introduction of non-fusion technologies like artificial discs, dynamic stabilization implants and nucleus replacement devices in the U.S., where 70 percent of global spinal revenues were generated in 2004.

The five largest companies in the global spine market – Medtronic Sofamor Danek, JNJ, Synthes, Stryker and Kyphon – controlled 80 percent of 2004 sales in this segment. However, competition has intensified in the spine segment more than any other and additional key contenders include Aesculap, Biomet, **Blackstone Medical**, **NuVasive**, **Spinal Concepts** and Zimmer.

Traditional spinal fusion incorporates the use of metallic (titanium or stainless steel) plate/screw systems for cervical applications and plate/screw, hook/rod/screw or interbody fusion devices for lumbar applications. More than 100 companies market these types of systems, many focused on geographic regions (e.g. **Solco Biomedical** in Korea, Showa Ika Kohgyo and Japan MDM in Japan; **Anatomica Spine**, **Bio-Prot**, **Co-Ligne**, **Medicrea**, etc. in Europe; **GMReis** and Ortosintese in South America; etc.), making the spine segment of the global orthopaedic market one of the industry's most competitive.

A comprehensive list of companies marketing spinal products can be found in Exhibit App-4 in the Appendices at the end of this overview.

Aside from traditional metals, structural allograft also plays a role in spinal applications, predominantly in interbody fusion devices as an alternative to metal and carbon fiber designs. Most spine companies have aligned themselves with tissue processors for distribution of allograft spacers and many also are developing alternative biologically based biomaterials for use in the spine. (See Orthobiologics.)

In Japan, ceramic-based devices play a key role in the interbody fusion market through such companies as **Pentax** with its Apaceram hydroxylapatite blocks. PEEK spacers, cages and other implants (manufactured by Invibio) have found increasing use among spine surgeons largely because their radiolucency allows the surgeon to visualize the status of the fusion. Most of the larger companies and a number of smaller players (e.g. Blackstone, Co-Ligne, **K2M**, **Signus**, Surgicraft, **Theken**, etc.) have incorporated PEEK or other polymers into their cages, vertebral body replacement devices and spacers. Signus and DePuy also offer devices manufactured from carbon-reinforced PEEK and other polymers.

Other materials that have found a place in spinal fusion include Zimmer's Hedrocel porous tantalum used in lumbar and cervical interbody fusion cages and vertebral body replacements and Biorthex's Actipore porous titanium-nickel alloy used in posterior lumbar and anterior cervical fusion devices. Biorthex is also developing anterior lumbar fusion and vertebral body replacement devices manufactured from Actipore.

Resorbables in spine come from **MacroPore Biosurgery**, whose Hydrosorb resorbable polylactide implants have been cleared for use in lumbar spinal cages in the U.S. and Europe. In 2005, Medtronic introduced its Mystique Resorbable Graft Containment Plating System (manufactured by MacroPore) for stabilization of bony tissue in cervical spine fusion in the U.S., making it the first company with such a product in the U.S. Also in 2005, Inion obtained CE Mark approval for its Inion S-1 Biodegradable Anterior Cervical System for use with adjunctive immobilization.

Aortech's high silicon content polyurethane copolymers include Elast-Eon, which may find a place in **Pearsalls**' disc products (acquired by NuVasive). Aortech and Pearsalls signed a non-exclusive technology license and material supply agreement for spinal applications with a focus on lumbar spine, although expansion into other orthopaedic areas remains possible.

SpineMedica obtained exclusive, worldwide license to use **SaluMedica**'s Salubria hydrogel in the development of the SaluDisc non-constrained lumbar total disc replacement device. Cervical products may be developed in the future.

Mekanika has developed its Modulus System, which incorporates a proprietary carbon fiber composite architecture and has application in rigid and compliant implants for use in spinal fusion and disc support.

While fusion remains the predominant procedure used to treat degenerative disc disease, it is not without its problems. For instance, fusion can lead to some loss of motion for some patients and it has been associated with the deterioration of adjacent vertebral levels. As a result, fusion may not be optimal for younger, more active patients. Herein lies the attractiveness of motion preserving technologies like artificial discs, nucleus replacement, dynamic stabilization, etc.

Disc replacement devices are available in more than 30 countries outside the U.S., where they have been used for decades. Despite their widespread availability, discs have not yet penetrated the spinal market, with estimates placing their use at just 20 percent of potential procedures. With the late 2004 FDA clearance of the first artificial disc in the U.S. – the Charité from **DePuy Spine** – many predicted overwhelming success of the device. Early estimates placed DePuy's Charité sales in 2005 at as much as $200 million. However, the company has faced significant barriers to use of its device, the most prominent being reluctance on the part of private insurance companies in the U.S. to reimburse for use of the device, as many consider it experimental despite FDA's clearance and Medicare's reimbursement for the device. At the end of June 2005, Charité had been used in fewer than 3,000 procedures in the U.S., far below expectations.

As DePuy deals with less-than-stellar sales of the Charité, the company will face competition in the U.S. in 2006, when Synthes expects to introduce its ProDisc lumbar disc replacement to the U.S. market. The first cervical disc products should enter the U.S. in 2007 through Medtronic, which likely will introduce a lumbar device in the same year. Stryker's FlexiCore lumbar disc could enter the U.S. market in 2009, pending appropriate FDA clearances, with the CerviCore cervical disc replacement commercialized by 2010.

As the larger spine companies introduce their artificial discs to the U.S. market over the next three years, a vast array of other companies have begun disc programs including **Abbott**, **Alphatec**, Amedica, **Axio-Med**, Biomet, Blackstone, **Custom Spine**, **Flexuspine**, **Globus**, **Highgate**, Impliant, K2M, **LDR**, **Life-Spine**, **Nexgen Spine**, NuVasive, Pioneer, **Pisharodi**, **Ranier Technology**, **SeaSpine**, Signus, **Spinal-Motion**, **Theken Spine**, **U.S. Spine**, **Vertebron** and **X-Spine**. Most of these companies will commercialize their products in the U.S. between 2008 and 2010, with European clinicals already underway for some.

Titanium/proprietary elastomer disc technologies are under development by AxioMed and **Theken Disc** for lumbar spine, with Theken's eDisc also incorporating microelectronics to collect and track motion and load data. **Takiron**'s lumbar disc features a woven polyethylene, while the NeoDisc cervical disc from Pearsalls (acquired by NuVasive) incorporates a proprietary polymer encapsulated in engineered embroidery of polyester.

Biomet's Rescue lumbar and cervical devices use pyrocarbon and polyethylene combinations and the company's Min T incorporates ceramics with titanium alloy. MoM technologies remain the focus of Medtronic, SpinalMotion and Stryker for cervical and lumbar applications, although Medtronic's Bryan cervical disc combines titanium with polyurethane. Vertebron's cervical disc will also feature MoM, as will X-Spine's X-DYNE device.

Before the end of 2005, **Scient'x** hopes to submit an IDE application to begin clinical trials of its Discocerv CoC cervical disc, which incorporates titanium alloy endplates embedded with ceramic bearing components. NuVasive filed to begin clinical trials in the U.S. with its anteriorly-approached CoC Cer-

pass Cervical Total Disc Replacement. SpinalMotion received conditional approval from FDA to begin clinical trials for its Kineflex lumbar and Kineflex-C cervical disc devices. The products have been implanted in more than 500 patients outside the U.S. since 2002 and, in the U.S., the company has enrolled more than 80 patients in cervical and lumbar disc trials.

Discs that combine cobalt chrome and polyethylene will be introduced by Globus, LDR and Synthes for lumbar applications, with Vertebron's lumbar disc technology centering on titanium and polyethylene. Globus entered IDE clinicals for its Secure-C cervical disc replacement products, and NuVasive could enter clinicals with the NeoDisc cervical disc by year's end. NuVasive anticipates that the NeoDisc could be available commercially in Europe by as early as 2007.

Within the next 12 months, AxioMed's Freedom lumbar disc, LDR's Mobidisc lumbar and Mobi-C cervical products (already used in more than 250 patients outside the U.S.), SpinalMotion's Kineflex lumbar and Kineflex-C cervical disc devices and U.S. Spine's Spartacus Lumbar Disc (non-linear fiber matrix) could enter U.S. clinicals. Pioneer Surgical could begin IDE studies in 2006 for its CE Mark approved motion-preserving artificial nucleus and Vertebron's Cervical Motion Preservation device could enter clinicals in 2006, as well.

Repair of the soft tissues of the spine will come from development efforts at **Anulex** and **Intrinsic Therapeutics**, with facet joint arthroplasty systems the focus of **Archus**, **Facet Solutions**, Impliant and **Quantum**.

In 2005, Anulex received FDA clearance to market its Inclose Surgical Mesh System, which comprises polyethylene terephthalate monofilament braid material preloaded on a disposable delivery tool. The implant provides a barrier and scaffold to facilitate the repair of soft tissue and could have application in repairing and sealing the annulus in herniated or otherwise damaged discs.

Archus initiated enrollment in a U.S. clinical trial and received CE Mark approval for its Total Facet Arthroplasty System, which replaces the facet joints, for treatment of spinal stenosis. In Europe, Archus will

enter the market through an investigational approach at prominent centers to accumulate clinical experience with the device.

Quantum Orthopedics expects to begin clinicals in the U.S. in 2006 with its MIS Zyre facet arthroplasty system. The Zyre device, which features a malleable spacer placed between the facet joints, does not violate the pedicle and, as such, maintains the option for fusion in the future. In addition, the device can be used either in conjunction with disc replacement or as a stand-alone implant.

The first clinical implantation of Facet Solutions' Anatomic Facet Replacement System occurred in the fall of 2005 in Brazil, while Impliant continues to develop its posterior motion-preserving TOPS (Total Posterior Spine) System based on the company's cushion bearing polyurethane technology. Clinical trials for the TOPS device are currently underway in Europe and a recent infusion of cash will help Impliant move forward with additional trials and regulatory clearances for the device.

U.S. Spine's Facet Fixation Gun also addresses issues with facets and includes a transfacet implant and MIS disposable delivery device.

In nucleus replacement, **Raymedica**'s hydrogel PDN-Solo prosthetic disc nucleus devices have been implanted in more than 3,500 patients worldwide and are cleared for use in all major geographic regions outside the U.S. The PDN-Solo implants feature a hydrogel material encased in a polyethylene jacket. The hydrogel replaces the function of the failed intervertebral disc, while the jacket maintains the size of the hydrogel. PDN devices are implanted in a dehydrated state and expand upon hydration. Raymedica is pursuing clearance for the device in the U.S.

Despite its having been on the market outside the U.S. for years, Raymedica has not yet entered the U.S. market and will face intense competition from a number of companies there. For instance, **Disc Dynamics** filed an IDE with FDA for its curable polyurethane Dascor implant in mid-2005. The product received CE Mark approval and was launched in Europe for treatment of herniated and degenerated lumbar discs.

Ranier produces the CAdisc (Compliant Artificial spinal disc), a polyurethane-polycarbonate graduated modulus device that mimics the biomechanical properties of the natural disc. Through its proprietary manufacturing process, Ranier is able to covalently bond the device throughout, thereby removing potential regions of high stress concentration.

Nexgen Spine's disc replacement products include the lumbar Physio-L and cervical Physio-C disc implants that feature elastomeric polycarbonate polyurethanes with varying stiffnesses, transitional polymer endplates and fluid filled nucleus cavities. Unlike the Ranier technology, Nexgen's manufacturing process does not allow it to create a single material device, but instead combines two materials into one device.

Zimmer's spiral shaped, polycarbonate/urethane elastomer Newcleus is involved in pilot studies in four centers in Europe, while **Replication Medical**'s NeuDisc radially anisotropic spinal nucleus implant is currently undergoing clinical evaluation in Europe. Replication, which has received funding from Synthes, **Johnson & Johnson Development Corporation** and, most recently, **Abbott Spine**, seeks to begin clinical trials in the U.S. in 2006 for the NeuDisc.

Orthonics seeks to further develop its hydrogel biomaterial and surface patterning technique used to create a more natural attachment between artificial material and bone or cartilage. The company believes that its technologies could be used to repair only the damaged portions of discs and may also eliminate the need for attachment screws. Further, the technology may have application in facet joint repair.

Spine Wave's NuCore Injectable Disc Nucleus incorporates an *in situ*, curing, injectable, recombinantly produced protein polymer for which the company has initiated preclinical studies to support the filing of an IDE with FDA. Spine Wave will expand European human clinical testing of the device.

Gentis has also developed a percutaneous nucleus replacement/augmentation device, which comprises DiscCell, an injectable implant that polymerizes *in situ*. Gentis will further develop not only the nucleus device but also cell-seeded second-generation products.

Corin will work with a consortium of institutions in the development of a Percutaneous Disc Nucleus device. The device will likely take the form of a bag filled with a special gel that would have the characteristics of a normal disc nucleus. Corin will have exclusive, worldwide rights to exploit the device, once fully developed and approved.

Novel spine therapies include **St. Francis**' X-Stop Interspinous Process Distraction System and NuVasive's ExtendSure interspinous dynamic stabilization product for treatment of spinal stenosis. **CG Surgical**'s Cervical Laminoplasty Plate System, for treatment of cervical spinal stenosis, features plates used to reconstruct lamina.

TranS1's AxiaLIF uses a percutaneous, para coccygeal axial approach to lumbar fusion, and could potentially be used in placement of disc nucleus devices, as well. TranS1 will slowly release its products to the U.S. market.

Innovative Spinal Technologies' (IST) tissue evacuation system uses vapor to remove nucleus material and the company has also developed a device that repairs annular tears.

In the MIS arena for spinal procedures, **Endius** has retained its focus on MIS technologies for discectomy and pedicle screw fixation, and in 2005, expanded its intellectual property portfolio through purchase of more patents specific to MIS access, instruments, implants and methods for establishing access and delivering implants to the spine. Endius acquired more MIS technologies and redesign of some of its instruments may accommodate motion preservation technologies. Procedures using the company's MIS technologies continue to demonstrate less blood loss, fewer complications and lower length of stay vs. some traditional approaches.

NuVasive's MIS technologies account for the majority of the company's revenues and include nerve avoidance and spine access systems, along with specialized implants. NuVasive's extreme lateral interbody fusion (XLIF) technology may be the first with application in the removal of failed artificial discs.

DePuy expanded its MIS offerings with a variety of instruments that address percutaneous screw and rod placement. **Life Spine**'s MIS offering includes an MIS pedicle screw system and MIS interbody fusion cages (under development), while Triage will further develop its Teleport MIS spine technology, which allows for implantation of facet fixators through increasingly larger dilation cannulae.

Endoscopic spinal access technologies remain the focus of Richard Wolf, **Myelotec** and **Joimax** (joined minimal access technologies). Wolf's systems allow for posterior, posterolateral and lateral percutaneous endoscopy and foraminotomy, while Myelotec's Visionary Catheter System provides an ability for surgeons to diagnose and treat spinal pathologies endoscopically. Joimax has developed the Thessys system for transforaminal posterolateral removal of herniated discs. Thessys may be applied to any MIS disc procedure.

IST's product portfolio includes navigated systems as well as MIS pedicle screw implantation technologies. Other MIS devices on the market include HydroCision's SpineJet Hydrosurgery instruments based on the company's fluidjet technology. SpineJet tools allow for the selective cutting and removal of soft tissue, making them suitable for disc space preparation in lumbar interbody fusion and for percutaneous microdiscectomy applications. In addition, Erbe markets its Helix Hydro-Jet instruments, which can be used in percutaneous discotomy and synovectomy. Erbe focused initially on ex-U.S. markets, but received FDA clearance in 2004. (The company's primary focus remains electrosurgery.)

Dynamic stabilization products on the market include Zimmer's Dynesys, Scient'x's dynamic TTL rod, Medtronic's DIAM, Synthes' FASS and the Wallis system from Abbott. None of these products is available in the U.S. as a dynamic system, although some have been cleared for use in fusion applications. Abbott expects to enter U.S. clinicals for the Wallis by the end of 2005.

Applied Spine Technologies' MIS M-Brace implant features traditional spinal screws in conjunction with a posterior dynamic stabilization technology. NuVasive will develop dynamic stabilization technologies it acquired in the assets and intellectual property of **RiverBend Design**. Paradigm Spine emerged through the combination of technologies from Fixano and Biorthex and its non-fusion products include

Coflex, an interspinous dynamically-functional implant (formerly the Interspinous U from Fixano) and the Orthobiom non-fusion alternative for treatment of adolescent idiopathic scoliosis.

N Spine has developed the Dynamic Posterior Stabilization Fixation for MIS approaches to spine procedures. N Flex, the company's "Flexible Fixation Device," provides for fusion or non-fusion through posterior MIS, while pedicle guidance system (cleared by FDA), tubular retractors and pedicle screw system complete N Spine's posterior MIS product offerings. N Spine has established a subsidiary in South Korea.

In summary, future growth in the global spine market will come with expanded use of BMPs, the introduction of artificial discs, increased adoption of MIS access tools and increased penetration of interbody fusion technologies into the spinal arena.

COMPUTER ASSISTED SURGERY AND ROBOTICS SYSTEMS

Computer assisted surgery (CAS) systems provide surgeons with interactive guidance to help them track instruments and implants in real time during surgical procedures. The systems are designed to optimize the intraoperative positioning of instruments and the placement of implants either with or without image guidance (IGS) provided through computed tomography (CT) scans, fluoroscopy, etc.

Interest in CAS systems began within the field of neurosurgery. However, over the past ten years, the technologies quickly moved into the areas of spinal fusion (to aid in the placement of pedicle screws), joint replacement (to minimize leg length discrepancy, improve accuracy of cuts, optimize positioning of components, etc.) and ACL repair (to optimize accuracy in tunnel and graft placement). Systems exist, as well, for high tibial osteotomy and fixation of difficult-to-reach and treat fractures.

Robotics systems in orthopaedics typically incorporate software used to program a workable robot, which serves as a tool to help surgeons prepare a site for introduction of an implant.

Acrobot's technologies center on the use of robotics and passive constraint navigation to create surgical systems for minimally invasive, bone conserving orthopaedic surgery. The company's Active Constraint Robot technology applies control to motorized, programmable devices allowing for "hands-on" robotics. Tools mounted on the Acrobot work in reaction to a surgeon's actions, but do not allow for movement outside a specified anatomical area.

Acrobot's Tubes Hip Resurfacing CAS System will be commercialized in conjunction with Corin for use with MIS implantation of the Cormet Hip Resurfacing system. The system (to be branded WayFinder) features proprietary pre-operative planning software and incorporates technologies to allow for specific soft tissue management and instrument tracking without relying on optical systems. Parts of the system have received CE Mark approval. As a technology platform, Tubes will be developed for application in other joints in CT-free and optical tracking versions.

Aesculap's OrthoPilot CT-free system received CE Mark approval in 1999, with its first application in total knee replacement. FDA cleared OrthoPilot for use in 2001 for total knee replacement and in 2002 and 2003, OrthoPilot was used in orthopaedic procedures in Korea, Japan, Taiwan and China. Today, OrthoPilot modules exist for ACL repair, acetabular cup placement, high tibial osteotomy and total knee replacement and, to date, OrthoPilot has found use in just under 44,000 hip and knee arthroplasty and ACL replacement procedures by more than 300 surgeon users worldwide.

Biomet has introduced different modules for its Acumen Surgical Navigation System, developed in conjunction with **Z-Kat** (now **MAKO Surgical**). The system (for MIS and traditional procedures) addresses hip and unicompartmental knee techniques, with additional modules to be released for total knee and spine procedures. The company continues to develop additional procedure-specific software for navigation in reconstructive and spinal areas.

Bonecraft's CAS initiative centers on the use of traditional X-ray images to create 3D computer-aided design models, using MRI and CT scans if more detailed information is needed. The software enables preoperative planning and rehearsal of orthopaedic surgical procedures, i.e., correction of acute and chronic bone deformities.

To date, approximately 1,990 **BrainLAB** image-guided medical technology systems have been installed in more than 65 countries. BrainLAB markets the VectorVision, a suite of CT-based and CT-free modules for joint replacement and trauma applications. BrainLAB's CAS portfolio features open platform architecture, allowing for use with a variety of companies' products.

For instance, BrainLAB's collaboration with DePuy resulted in the introduction of DePuy's Ci System, a fully integrated surgical package of hardware, software and instruments for MIS total knee replacement. BrainLAB and Biomet will work toward development of VectorVision for Biomet's hip and knee products and an agreement between BrainLAB and Wright will lead to integration of Wright's Medial Pivot and other knee systems within BrainLAB's CT-free VectorVision system for both traditional and MIS approaches. BrainLAB has also developed a specific VectorVision hip SR system for hip resurfacing using Smith & Nephew's Birmingham hip.

Waldemar Link, in conjunction with BrainLAB, has developed non-CT-based navigation for hip and knee implants, while Synthes and the **AO Foundation** will work in partnership with BrainLAB to further develop the use of VectorVision in spine, trauma and maxillofacial applications, while also providing training for surgeons.

CAS Innovations has developed the CAPPA (Computer-Assisted Planning and Positioning Applications) product family, which incorporates preoperative 3D planning with an open-interfaced, modular navigation system. CAPPA has been used for CT-free hip and knee replacement and implantation of Corin's Cormet MoM resurfacing hip with the CAPPA SURFACE system.

Through its acquisition of **Cbyon**, **GE Healthcare**'s CAS portfolio now includes Image-Enhanced Fluoroscopy modules designed specifically for spinal applications. The technology tracks and displays instruments along with a dynamic display of subsurface critical structures, creating a more 3D view. GE's CAS platform also features the InstaTrak surgical navigation system for MIS procedures in orthopaedic and trauma applications.

DePuy Orthopaedics' iZone Orthopaedic Operating Room of Tomorrow includes the Ci System, an intraoperative IGS system that features wireless communication between computer, data acquisition array and instruments. The design of the system minimizes interference from additional hardwired instrumentation. The Ci technology is available for use with total and unicompartmental knee systems.

Robotics in orthopaedics has remained the focus of **Integrated Surgical Systems**, whose ROBODOC Surgical Assistant System for hip and knee replacement has been in use outside the U.S. since 1992. The system features a computer-controlled surgical robot equipped with specialized drill bits and other hardware (e.g. the ORTHODOC workstation) for preparing bones for prosthetic implants. Numerous implant companies have signed agreements with Integrated Surgical for use of their implants with the ROBODOC system, which has been used in more than 15,000 surgical procedures. Despite more than a decade on the market, ROBODOC has made few inroads into any market and, in late 2004, the company faced a lawsuit from patients in Germany who claimed that the ROBODOC is defective and dangerous.

MAKO Surgical develops CAS navigation technologies, robotic bone sculpting and other MIS orthopaedic systems. The company's frameless, multi-modal Acustar Imaging Marker system has been cleared for use in the U.S. and Europe. MAKO will further develop MAKOplasty, a human-assisted robotic system targeted at early-stage knee treatment. The system allows surgeons to digitally sculpt and preserve bone tissue through small portals and place instruments and implants. The platform includes both a robotic system (cleared by FDA in 2005) and a knee implant. Human clinicals for the system could occur before the end of 2005, with launch in the U.S. in 2006.

Mazor Surgical Technologies markets the SpineAssist, a miniature robotics system for spine applications in the U.S. and Israel. The company also recently received FDA clearance for the Hover-T Bridge, used in conjunction with the SpineAssist. The Hover-T Bridge attaches percutaneously to the lumbar spine and "floats" above the spine. The device is then attached to SpineAssist, allowing the surgeon to navigate along the spine and access any point in the spine through MIS approaches. The surgeon can then insert implants and instruments.

Mazor is currently developing platforms for other MIS techniques in the spine for such procedures as transfacet fixation, tumor excision and vertebroplasty/kyphoplasty; and will develop other orthopaedic applications of its technology including an IM nail guidance system (NailAssist) and one for total knee replacement (KneeAssist).

Medtronic Navigation (formerly **Medtronic Surgical Navigation Technologies**) essentially led the charge for IGS in spinal applications with the development in the early 1990s of its StealthStation Treatment Guidance Systems. Approximately 2,000 StealthStation systems have been installed in more than 600 institutions worldwide for use in neurosurgery, cranial, spinal and ear/nose/throat procedures.

Medtronic and Zimmer will work together to develop CAS for MIS joint replacement, while Navigation's other technologies offer an open platform for use with a variety of manufacturers' implant systems. Medtronic also serves as co-marketing partner for distribution of Z-Kat's Acustar implantable fiducial markers.

ORTHOsoft's CAS initiatives center on the company's Navitrack systems, which include hardware, software, instruments, cameras, etc. with CT-based, CT-free and fluoroscopy-based modules for hip replacement, knee replacement, pedicle screw placement and ACL reconstruction procedures. Over the past ten years, the Navitrack technology has supported more than 16,000 procedures in Europe and the U.S. (including the placement of more than 2,500 pedicle screws).

A five-year worldwide co-development and distribution agreement between ORTHOsoft and Smith & Nephew has resulted in the development of the AchieveCAS MIS hip and knee systems adapted for Smith & Nephew's key product lines. ORTHOsoft and Zimmer are collaborating on Navitrack hip, knee and spine applications for Zimmer implants and Zimmer's imageless application for the Navitrack TotalHip. In addition, the companies will develop CAS systems for non-minimally invasive knee, hip and spine implant surgery, with Zimmer handling global distribution of any resulting products.

Through its collaboration agreement with Medtronic, ORTHOsoft will provide development expertise for advancing Medtronic's Universal Orthopedic Navigation program. Medtronic holds distribution rights to the Zimmer ORTHOsoft hip and knee applications on its StealthStation guidance system.

In early 2005, ORTHOsoft launched its Navitrack Sesamoid, a compact, portable and simplified CAS system that is not only one-third the weight of the "regular" system less the stand, but reportedly also saves on customers' investments in CAS systems.

PI Systems offers the PiGalileo CT-free CAS and navigation modules for hip and knee replacement applications. **PLUS Endoprothetik**, one of PI Systems' sister companies, launched the PiGalileo system in the U.S. for use with its TC-PLUS Solution knee. Worldwide, the systems have been installed for use in more than 10,000 procedures.

Praxim Medivision (which acquired Synthes' **Medivision CAS** division) entered into an agreement with **Precimed**. The companies will integrate IGS technology in support of the UKI, a femoral knee cutting guide along with IGS solutions adaptable for use with any total knee implant. Mathys' non-image-based balanSys kneelogics navigation system also resulted from a collaboration with Praxim.

Precision Instrument Systems' mini-robot uses infrared rays along with computer navigation to place cuts on patient bone.

Recently purchased by Integra, **Radionics** offers a variety of neurosurgery CAS systems, but competes, as well, in orthopaedics/spine with its 3D wireless SpinalSight Spinal Module.

Siemens Medical Solutions offers the SIREMOBIL Iso-C3D, reportedly the world's first mobile C-arm with 3Dimaging that comes equipped with NaviLink, a 3D navigation interface. The technology allows for real-time CT scans to be transferred directly to navigation systems, obviating the need for any registration of anatomy.

Stryker's CAS line combines software, wireless instruments and infrared cameras to provide navigation through a variety of fluoroscopy-based, CT-based and CT-free systems for numerous orthopaedic procedures. Navigation modules from Stryker include those for standard and MIS total hip and total knee replacement; pedicle screw placement and internal fixation of pelvic, femur and tibia fractures, placement of lag screws and entry point navigation and distal locking for IM nails. In 2004, the company launched new cart and camera systems in addition to new imageless platforms for total hip and uni and total knee.

Others with navigation systems include Ceraver Osteal (Ceravision for knee), Eska (CT-free Knee Surgetics), Kinamed (image-free NaviPro system for any hip system) and Medacta (Navigation System MNS CT free navigation for total knee arthroplasty).

ORTHOBIOLOGICS

"Orthobiologics" refers to products that incorporate biology and/or biochemistry for the repair, replacement or regeneration of musculoskeletal structures. Products considered "orthobiologic" include bone and soft tissue substitutes, allograft bone/tissue, tissue-engineered substances, growth factors/bone proteins, stem cells, etc. The following section provides a review of companies with either commercialized orthobiologic products or orthobiologic initiatives in place.

A comprehensive list of companies marketing biologics and cements can be found in Exhibit App-5 in the Appendices at the end of this overview.

3DM is developing PuraMatrix synthetic peptide hydrogels for use in orthopaedic applications (e.g. bone fill, spinal fusion, implant coatings, drug delivery). Pre-clinical safety and efficacy testing is complete in animal studies. The company plans to submit the bone fill indication to FDA in 2005, with human clinicals for remaining orthopaedic applications to follow later.

aap Implantate markets two bone graft products – Cerabone, an HA-based bone substitute material available in granules and blocks, and resorbable PerOssal (a.k.a. Ostim), a nanotechnology-based calcium

phosphate bone substitute material with application in both weight bearing and non-weight bearing indications (trauma, orthopaedic, oral and maxillofacial surgery).

Aastrom Bioscience's orthobiologic platform centers on Tissue Repair Cells (TRCs), which are produced from small samples of bone marrow enriched for early-stage stem and progenitor cells that can form bone and other tissues. A typical TRC product contains a >80-fold increase in bone-forming cell types.

TRCs, combined with allograft matrices provided through collaboration with **Musculoskeletal Transplant Foundation** (MTF) and **Mathys Medical**, are currently involved in five clinical trials, three in the U.S. and two ex-U.S. The trials are designed to evaluate safety and effectiveness in the regeneration of new bone in the repair of long bone nonunion fractures and fresh nonunion fractures. The company is preparing an Investigational Device Exemption for TRCs in spinal fusions. Further, Aastrom plans to register TRCs in the European Union for use in bone graft surgery.

Abbott Spine's orthobiologics product activities arise from its acquisition of Spinal Concepts and **Spine Next**. From Spinal Concepts, Abbott Spine distributes **Curasan**'s Cerasorb for spinal indications and a line of specialty allograft products for spinal applications, while Spine Next markets NovaBone products in the U.S.

ACell develops, manufactures and markets products based on naturally occurring biological scaffolds. The company's urinary bladder matrix (initially targeted at veterinary applications), derived from the lining of urinary bladders of specially bred pigs, is an extracellular matrix scaffolding that has shown promise for healing equine tendon and ligament injuries.

Acologix' lead orthobiologic product is AC-100, a compound that has demonstrated potent and selective bone and dental formation activities *in vitro* and *in vivo*. The company will initially target AC-100 for the treatment of osteoporosis, with additional indications in local bone regeneration. Having completed a first Phase II clinical study, Acologix initiated an additional Phase II clinical study of AC-100 for the treatment of periodontal bone loss. In addition, the company will further investigate Ossomar, a novel class of

compound that has been shown to increase bone mass and mechanical strength, while retaining normal, healthy bone morphology.

Through technologies that rapidly convert images of good bones to 3D virtual images of needed replacement bone segments, **Advanced Ceramics Research** can create "Plasti-Bone," micro-porous calcium phosphate-coated polymer "bones." The product's first uses will likely target small bone areas, although replacement of entire load-bearing bone segments may come in the future. Proof that the process works has been shown in animal testing as well as in tissue cultures.

Aesculap's orthobiologics franchise includes Novocart autologous chondrocyte transplantation (ACT; available outside the U.S. and provided through a relationship with **TETEC**), ProSpace allograft spacers for spinal indications, and demineralized bone matrix (DBM) available in the U.S. as DynaGraft II through the company's non-exclusive distribution agreement with **IsoTis OrthoBiologics**.

Affinergy specializes in peptide-based coatings that bind to biological and synthetic materials to enhance the performance of medical devices. In orthobiologics, the company's technologies could be used for attaching growth factors to metals (e.g. for joint replacement or fracture repair) or for creating scaffolds for tissue engineering/regeneration (e.g. tendon, ligament, etc.).

AlloSource remains a key supplier of allograft used in orthopaedic procedures, such as AlloFuse DBM, AlloMatrix DBM Putty and Gel, etc. The **Joint Restoration Foundation**, comprising AlloSource and **LifeLink Tissue Bank**, focuses upon processing technologies and the promotion of beneficial uses of joint restoration allograft tissue. AlloSource claims to be the first tissue bank to process and distribute 100 percent sterile soft tissue allografts using a low dose, low temperature gamma irradiation process that reportedly does not alter the biomechanical, structural or functional properties of allografts.

Alphatec Spine purchased all assets of Cortek, whose orthobiologics franchise centers on the use of novel structural allografts for spinal fusion applications. The company markets cervical and lumbar allograft systems along with "composite" allograft constructs that incorporate both cortical and cancellous bone. Through an alliance with Biocomposites, Cortek will submit an IDE with FDA and for CE Mark

approval of Replace, a resorbable interbody device incorporating Biocomposites' Biosteon with a synthesized calcium phosphate. Cortek has also developed a product for vertebral compression fractures and may obtain clearance for the device by 2006.

Angiotech Pharmaceuticals executed a license agreement to **Histogenics** for use of Angiotech's ChondroGEL biomaterial in cartilage, ligament, meniscus and tendon repair, including related osteochondral defects. With its proprietary Tissue Engineering Support System, Histogenics grows cell matrices of patient cartilage known as NeoCart. ChondroGEL, a collagen-modified hydrogel, has been shown in preclinical studies to support healthy cartilage regeneration while fixing cartilage implants, such as NeoCart, into place. NeoCart is currently undergoing an FDA Phase I Investigational New Drug study.

Angiotech has developed an injectable form of paclitaxel known as PAXCEED, and is investigating applications in cartilage preservation and the prevention of scarring in joints. In preclinical studies, paclitaxel demonstrated the ability to reduce fibrous tissues caused by overgrowth, reduce inflammatory response and protect cartilage.

Angström Medica's FDA-cleared NanOss calcium phosphate uses nanotechnology to achieve high degrees of strength while remaining osteoconductive. The company is focused on developing NanOss in structural, injectable and bioactive coating formats, with applications in sports medicine, trauma, spine and general orthopaedics.

ApaTech's products include ApaPore, a synthetic phase-pure porous HA; Pore-Si calcium phosphate bone graft substitute; and Actifuse silica-based synthetic bone graft. ApaPore and Pore-Si are cleared under the CE Mark for use in all orthopaedic applications (i.e. spinal fusions, bone tumors, fractures and in the replacement of failed or loose joint prostheses), and all three products have obtained FDA 510(k) clearance for use in bony voids/gaps that are not intrinsic to the stability of the bony structure of the skeletal system, i.e. in the extremities, spine and pelvis. Clinical studies of Pore-Si are underway in Germany and the U.K., with an initial focus on spinal fusion.

ApaTech opened U.S. operations to develop and market its products. **Global Orthopaedic Technology**, **PO Medica** and Surgicraft distribute ApaPore and Pore-Si in Australia, Sweden and the U.K., respectively.

ARS Arthro has developed CaReS for treatment of focal articular cartilage defects in the knee joint using ACT. The company claims that its matrices provide significant benefit over existing ACT scaffolds. ARS expects to treat 5,000 patients in Germany with the technology during 2005, and expects that 300 patients will be treated annually in Turkey beginning in 2006 through collaboration with **Arthro Turkey Biotechnology**. The company hopes to produce CaReS-based products for meniscus replacement and ligament regeneration, as well.

ARS Arthro received FDA approval of an Investigational New Drug application for CaReS and, following a pilot study beginning in 2005, expects to commence an additional multi-center comparative trial in preparation for a possible commercial registration in 2006.

Artecel's intellectual property portfolio centers on the area of adipose-derived adult stem cells. Research conducted with Artecel has shown that cartilage cells can be created from fat removed during liposuction procedures and that a hypoxic environment spurs chondrocyte differentiation. The company anticipates that it may be able to remove fat from a patient and use it to grow customized, 3D pieces of cartilage for implantation into the patient.

Articular Engineering's products contain tissue that has been engineered using the ARC (Alginate-Recovered Chondrocytes) method. With a focus on orthopaedics, the company will develop articular cartilage for use in repair of damaged joint surfaces, products for restoration of intervertebral disc properties following herniation and drug delivery therapeutics, all based on the ARC technology.

Berkeley Advanced Biomaterials (BAB) develops HA, TCP and other calcium-based products. The company's Ostetic line – Bi-Ostetic and Cem-Ostetic – represents its first foray into orthobiologics. Both Bi-Ostetic, a resorbable HA/TCP "composite" available in granule and block forms, and Cem-Ostetic, a proprietary formulation of calcium-based compounds available in powder and putty forms, received mar-

keting clearance in the U.S. and European Union. Both are indicated for use in defect filling in extremities, pelvis, spine or cranium. Berkeley has received FDA 510(k) clearance for its Marrow Plus (M+), BioPlus and Generos bone void fillers. Blackstone Medical distributes Berkeley's bone graft substitutes for spine surgery applications, while Orthofix markets and distributes a line of resorbable bone repair biomaterials engineered by BAB for trauma and reconstruction under the OsteoMax brand.

BioAfix, a wholly owned subsidiary of **Schwartz Biomedical**, intends to begin proof-of-concept testing for its technology for regenerating meniscus tissue that has deteriorated with age. The company's repair mechanism centers on ensuring sufficient blood flow to support healing by applying growth factors to a patient's own cells, and mounting these on a bio-derived or synthetic scaffold. The company could have a product commercialized in the U.S. by 2008.

Biocomposites develops, manufactures and markets synthetic calcium composite products for bone regeneration as well as resorbable composite technologies for sports medicine applications. The company's bone products include Stimulan, a calcium sulfate bone void filler cleared in the U.S. and Europe; CE marked Allogran-R, a resorbable, synthetic porous granular TCP matrix for defect filling applications; Allogran-N, an HA for use in conjunction with allograft in impaction grafting techniques in revision joint replacement procedures (CE marked); and Genex, an FDA-cleared resorbable calcium sulfate bone graft product for bony voids or defects/gaps that are not intrinsic to the stability of the bony structure. The product can be injected, packed or molded.

Through an exclusive, worldwide agreement, Biocomposites and Cortek collaborate on the development of next generation interbody fusion devices for spinal surgery, including resorbable implants that incorporate Biosteon with a synthesized calcium phosphate.

BioDelivery Systems has developed Transportor biomaterials, which can be formulated for particular applications, and the CellTran disposable MIS instrument, which can deliver not only Transportor biomaterials but also highly viscous surgical materials (e.g. gels, cements and bone slurries). Applications suitable for Transportor biomaterials placed with or without the CellTran instrument include bone defect filling and joint repair or regeneration.

BioLok received a patent for BoneGen TR time-released calcium sulfate, with application in the filling of all sizes of bony voids. The calcium sulfate is coated with PLLA (polylactic acid, polymer), and since both calcium sulfate and PLLA are individually cleared for internal use, the company expects no problems with rapid regulatory clearance for the two combined.

Biomet's orthobiologic franchise runs the gamut from bone graft substitutes to soft tissue reinforcement and platelet-rich plasma devices. Products marketed in the U.S. include the Calcigen line for general defect filling (Calcigen NaP calcium sodium phosphate, Calcigen S calcium sulfate and Calcigen PSI calcium phosphate), Mimix (HA/TCP) for repair of cranial defects, the OsteoStim line (resorbable calcium phosphate granules for spinal applications, DBM putty and allografts in a variety of configurations), Pro Osteon synthetic bone graft (HA and resorbable HA/calcium carbonate composite formulations used in the repair of skeletal defects including those in the spine), BonePlast resorbable calcium sulfate powder bone void filler, InterGRO DBM-based putty and the OSS Bone Graft System and OSS Rapidset Bone Graft.

Biomet's EBI subsidiary has a non-exclusive U.S. license to market **Millenium Biologix**'s Skelite resorbable calcium phosphate bone graft material for general defect filling, while its Arthrotek subsidiary distributes sports medicine allograft products and the CuffPatch, a FortaFlex-based rotator cuff repair patch developed through an agreement with **Organogenesis**. The bioengineered matrix technology may also lead to development of an arthroscopic ligament product.

EBI's franchise also includes the ACCESS System through which a surgeon draws a patient's blood and separates and processes its platelet-rich components. The resulting concentrate contains the patient's growth factors, which can then be mixed with bone substitutes. Biomet's **Cell Factor Technologies** subsidiary network also distributes the GPS (Gravitational Platelet Separation) System, which collects platelet concentrate (containing growth factors) from the patient's blood for reintroduction.

Outside the U.S., Biomet distributes Calcibon (calcium phosphate) in putty and granule forms; Collapat (collagen/HA), a fleece hemostatic bone substitute; Colloss, a resorbable collagen lyophilisate derived from cortical diaphyseal bovine bone; Endobon (bovine HA) blocks, cylinders and granules; and Tar-

gobone, an antibiotic-laden collagen lyophilisate. All are indicated for use in a broad range of orthopaedic applications.

BioMimetic Therapeutics' lead technologies center on recombinant human platelet-derived growth factor BB (rhPDGF). A worldwide supply agreement with **Orthovita** gives BioMimetic supply of Orthovita's proprietary Vitomatrix resorbable β-TCP scaffold to be used with BioMimetic's rhPDGF for dental, periodontal, oral and CMF grafting applications. BioMimetic's initial product – GEM 21S – combines rhPDGF with β-TCP for treatment of bone defects of the jaw. The company will work on preclinical and clinical development of its multi-product pipeline directed towards orthopaedic applications (i.e., therapeutic products combining tissue growth factors and bone allograft and those for the treatment of open and closed fractures, vertebral compression fractures and sports medicine applications such as cartilage, tendon and ligament repair). BioMimetic recently received FDA 510(k) clearance for its OsteoMimetic Synthetic Bone Matrix, a calcium compound bone void filler.

Researchers with **BioSET** (BioSurface Engineering Technologies) and **Brookhaven National Laboratory** developed a synthetic peptide that enhances the effects of BMP-2. Low doses of the peptide in combination with low doses of BMP-2 strongly triggered the development of bone-forming cells. Collaboration between the two groups could lead to replication of human growth factors with the potential to enhance the body's healing capabilities, especially when combined with orthopaedic implants.

BioSET entered into a collaborative technology evaluation and development agreement with EBI, under which the companies will evaluate one of BioSET's synthetic growth factor peptides in preclinical models. The agreement focuses on tissue healing and regenerative applications across multiple orthopaedic fields, and the license granted under the agreement is available to all affiliates of EBI.

BioSyntech's core platform technology centers on the BST-Gel family of injectable, *in situ* ionic polysaccharide gelling materials that retain genes and growth factors and effect their controlled release. The thermosensitive gels, which are liquid at room temperature, solidify at body temperature, allowing for injectability of the gels through minimally invasive approaches. The company's research and development activities include investigation of arthroscopically-delivered BST-CarGel for treatment of chondral

defects. In preclinical *in vivo* experiments, CarGel demonstrated its ability to guide the body toward successful regeneration of hyaline cartilage, and in an animal study, the product demonstrated the ability to deliver bone morphogenic proteins in a matrix that preserved their biological activity and maintained the BMPs at the delivery site. BioSyntech received CE Mark approval for CarGel and signed with a contract research organization that will support BioSyntech in its clinical trials. The company has applied for clearance of a pivotal clinical trial for CarGel in Canada to assess effectiveness in knee cartilage repair, and intends to add European sites under this protocol.

Also in development at BioSyntech are BST-InPod, an injectable product engineered for treatment of heel pain, for which the company is preparing a Canadian controlled clinical trial in anticipation of North American regulatory clearance; BST-OssiFil injectable self-gelling composite for bone grafting; injectable, self-hardening BST-OssiFix bone materials for restoring structural integrity (e.g. for vertebral fractures); an antibiotic in BST-Gel for treatment of bone infection; and BST-Disc, a liquid gel injected into the disc. BioSyntech has undertaken a study of long bone repair using BST-Ossifil in collaboration with an unnamed European bone substitute firm.

BioTissue Technologies has developed tissue engineering technologies that include autologous transplantation of cells grown by the company, which are then implanted into resorbable 3D scaffold-like structures. The company's BioSeed-C, an autologous 3D chondrocyte graft, is used in the treatment of damaged knee cartilage along with its autologous bone technology, BioSeed-Oral Bone, which is used in jaw bone replacement. The company continues to investigate development of other types of cartilage, a two-layer autologous bone/cartilage graft, stem cells/gene therapy (in collaboration with its subsidiary **TransTissue Technologies**), and an injectable bone replacement material that would incorporate autologous cells with a fibrin glue.

Bone Solutions' key initial focus is the commercialization of its adhesive bone technology, which comprises potassium phosphate, magnesium oxide and TCP and which is undergoing *in vivo* studies to affirm indications of bone formation. When mixed with water, the biomaterial can be injected or molded. In testing, the product has demonstrated adhesive qualities proven to attach ligaments and tendons to bone and

could be used as a substitute for the screws, other fasteners and bone cements and for the delivery of stem cells, growth hormones, proteins and other biologics.

Bone Support's development portfolio includes patented concepts for injectable, porous, resorbable bone materials (sulfates and HAs). The company's first product, SpineSupport, focuses on treatment of osteoporotic fractures. HipSupport, the company's second development program, centers on using injectable ceramics to augment repair prior to hip fracture procedures.

Bone Support is also developing Cerament, a porous osteoconductive material. Cerament Bone Void Filler is slated to enter a single-center study in patents undergoing radius osteotomy in late 2005. In Germany, follow-up is underway in a multicenter trial of Cerament SpineSupport in patients with one to two osteoporotic vertebral fractures, while in Sweden the product has entered an open-label pilot study in osteoporotic patients with acute single vertebral fracture.

BoneTec Corporation's technology relates to a proprietary method for preparing Osteofoam, a biodegradable polymer (poly (lactice-co-glycolide)) foam, which provides a framework for tissue growth. Applications for Osteofoam include spinal fusion and craniofacial and trauma procedures, while research and development efforts will expand into cell technologies targeted at selecting, growing and seeding human mesenchymal cells onto the Osteofoam scaffold.

CAM Implants markets CAMCERAM synthetic bone substitute, a 60/40 ratio of hydroxyapatite/ß-tricalcium phosphate that has received FDA 510(k) clearance. The product is currently distributed by CAM or its local distributors in Finland, Greece, India, Saudi Arabia, South Korea and Turkey.

CellGenix developed ARTROcell autologous chondrocyte preparations, which are manufactured by the company's Metreon subsidiary. Ormed distributes these ACT products in Germany for repair of cartilage defects in the knee, with Geistlich handling distribution in other parts of Europe. CellGenix and Geistlich are also cooperating in research and development of cartilage and bone regeneration.

Ceramisys has developed PermaBone and ReproBone for bone void filling in orthopaedic and maxillofacial applications. The company received CE Mark approval of the non-resorbable HA and resorbable HA/TCP products, available in block and granule formulations as bone void fillers for a range of non-load bearing orthopaedic applications. Ceramisys will pursue clearances to distribute its products outside of the European Union.

CeraPedics is developing a bone substitute and an implant coating using P-15, a synthetic small peptide attachment factor that mimics the cell-binding domain of collagen found in autograft bone. Preclinical and pilot clinical data suggest that the company's CerOss P-15 bone substitute could be superior to allograft and synthetic materials, and equivalent to autograft bone in orthopaedic applications. CeraPedics filed for an Investigational Device Exemption to study the use of P-15 in spinal fusion.

Ceraver Osteal's calcium phosphate products include CALCIRESORB and CERAPATITE. Calcium sulfates under development include CERAPLAST calcium sulphate pellets, CERAPLASTGENTA, CERAPLAST CMT (sulfo-calcic cement, low or fast cure) and CERAPLASTGENTA CMT.

Co.don's technologies involve the transplant of autologous cells. For instance, its chondrosphere removes damaged cartilage cells, grows them in a serum created from the patient's blood and reinjects them into the patient's joint. Evaluation of animal study revealed the feasibility of cartilage regeneration in osteoarthritic joints and the minimally invasive therapy of large articular cartilage defects. Co.don's chondrotransplant is an autologous bone cell transplant used to treat bone fractures, tumors, pseudoarthrosis, etc., with additional indications in disc degeneration. Co.don has also developed chondrotransplant DISC, an autologous disc cell transplantation technology indicated for treatment of acute, herniated intervertebral disks. **Bioengi** markets co.don's products in Italy, and chondrotransplant DISC is available for private patients in Germany, Austria and Switzerland. The company is pursuing U.S. partners for product clearance and distribution. Items in co.don's pipeline include osteotransplant DENT for oral maxillofacial surgery, and osteotransplant BONE for treatment of bone substance loss and nonunion fractures.

Collagen Matrix's technologies isolate and purify intact collagen fibers, and the company engineers intact collagen fibers into extracellular matrices in porous, tubular, membrane, filament and fibrillar forms.

Potential applications of the company's technologies include development of cartilage, ligament and tendon, bone, tissue augmentation and nerve patches and delivery systems for growth factors, gene therapy, etc. The company received CE Mark approval for its resorbable, flexible Collagen Bone Healing Patch indicated for use at both the implant site and the autograft donor site in bone graft procedures (e.g. cranial, maxillofacial and iliac crest). Certain of the company's synthetic bone grafting materials have also been cleared by FDA for use in oral surgery applications, as has its Osteoguide anorganic bone graft material which is derived from bovine cancellous and cortical bone.

Competitive Technologies granted **Soteira** an exclusive license to manufacture and sell products employing its patented injectable calcium phosphate-based nanotechnology bone biomaterial for use in spinal applications. The material is a flowable, moldable paste that may be used for both weight bearing and non-weight bearing bones. Competitive Technologies also has an exclusive agreement with the **University of South Carolina Research Foundation** to license and commercialize the biomaterial.

Corin markets BioFuse in Europe. BioFuse is a semi-resorbable HA/TCP composite available in bars, cylinders and granules for general orthopaedic applications.

Covalon Technologies received European Patent protection for drug delivery technology concerning the use of liposomes within a collagen-based hydrogel. The hydrogel may contain a variety of deliverable agents such as antibiotics, hormones, growth factors, etc., and the technology may have application in implantable medical devices. Further, the company has successfully cultured cells on its collagen/gelatin scaffold, and will begin research and development on the scaffold's use in tissue regeneration.

CrossCart has developed a patented technology that may eliminate the immunological rejection of animal tissue transplanted into humans. The company intends to develop, manufacture and market ligament, cartilage, soft tissue and bone replacement products based on its technology. Z-Lig, CrossCart's first product, is designed for ACL reconstruction and is currently in human clinical trials.

CryoLife received accreditation by the American Association of Tissue Banks in 2005. The company processes cryopreserved (CryoGraft) menisci; Achilles, patellar, semi-t/gracilis and posterior/anterior

tibialis tendons; osteoarticular allografts and osteochondral grafts. The company has also developed BioDisc, a protein-based hydrogel spinal disc nucleus repair system that preserved range of motion and provided stability over denucleation alone in preclinical studies. Also in 2005, the first human implantations of BioDisc occurred as part of a feasibility study in the U.K. The company expects to enroll additional patients in this study.

CryoLife's high-dose irradiated human orthopaedic tissues will be labeled sterile, based on a comprehensive validation process that was completed in mid-2005. The tissues are irradiated under a patented gamma-based process that is licensed from **Clearant** and is designed to substantially reduce microbial contamination and other pathogens in the processing of human orthopaedic tissue allografts, while maintaining tissue integrity. CryoLife's technology allows allografts to be stored and used for up to two years, permitting the company to completely review a donor's medical history before releasing the tissues for use. The company plans to introduce Process-treated cryopreserved patellar, tibialis, Achilles, quadriceps and peroneus tendons to orthopaedic surgeons for knee reconstruction.

In orthobiologics, Curasan markets Cerasorb β-TCP, which was certified in Europe as a carrier for patients' own platelet-rich plasma and received pan-European regulatory approval in block form for treatment of larger defects in weight-bearing areas. FDA cleared the product in 2002. Ascension Orthopedics holds exclusive license for U.S. distribution of Cerasorb Ortho, covering granules and block forms for orthopaedic applications with the exception of the spine, while Spinal Concepts distributes the product for spinal indications.

Curasan is also conducting research into the use of Cerasorb with 3D printing technology for rapid prototyping of custom patient-specific implants.

Cytomedix entered into a second licensing agreement with DePuy Spine for use of Cytomedix' Knighton patent for all applications of its autologous platelet releasate therapy (with some exclusions). DePuy Spine's existing exclusive licensing agreement for spinal, orthopaedic and neurosurgical applications will convert into a non-exclusive license to practice in those fields. Medtronic settled a patent dispute with Cytomedix and was granted a license for the Knighton patent for all applications of its autologous platelet

releasate therapy. Cytomedix' AutoloGel system, derived from the releasates, utilizes a gel composed of multiple growth factors and fibrin matrix.

The orthobiologic research initiatives of **Cytori Therapeutics** center on the use of adult stem cells (including those derived from fat) to treat disorders of bone, cartilage, etc. The company's point-of-care adipose (fat) tissue extraction system is FDA-cleared, and the company will continue to investigate applications for adipose-derived regenerative cells in bone repair and spinal disc regeneration.

In a case study, stem cells from a pediatric patient's own adipose tissue were combined with autograft bone, applied to a skull defect and set in place with resorbable MacroPore Protective Sheets. At three months, CT scans revealed new bone formation and near-complete calvarial continuity around the trauma area.

Doctors Research Group has developed Kryptonite, a calcified resorbable polyurethane available in granule, putty, paste and injectable formulations. DRG received clearance to market the product in Europe and South America and will seek U.S. clearance for load and non-load bearing applications, including a vertebroplasty indication.

Doxa has developed a calcium aluminate hydrate bone substitute material. Upon contact with body fluid, apatite forms at its surface creating immediate chemical bonding with bone. The resulting structure has strength on the order of cortical bone. The injectable biocement has application in bone replacement due to osteoporosis or cancer and Doxa has also developed a technique for depositing the material on the surface of implants. During 2004 Doxa commenced a clinical trial on the use of it bone substitute in the repair of distal radius fractures through minimally invasive injection. Upon application, the material reportedly achieves a complete chemical integration between itself and bone. Further trials are planned for vertebral compression fractures and other orthopaedic and spinal indications.

Etex's first orthobiologic product is α-BSM Bone Substitute Material, distributed in the U.S., Canada and Australia for the treatment of bone voids. DePuy and Biomet distribute α-BSM for certain orthopaedic and CMF applications.

The Etex pipeline includes bone graft substitutes suitable for reconstruction of skeletal defects; carrier compounds for delivering growth factors or therapeutic agents for various orthopaedic and spine indications; resorbable calcium phosphate-based devices (e.g. bone plugs, fixation screws and interbody spacers); and ultra-thin calcium phosphate coatings for implant surfaces or as agents for surface delivery of proteins and antibiotics. Etex has performed preclinical studies of its coatings technology in canine total hip replacement, canine dental screw implant and sheep interbody stabilization. Etex collaborates with **Wyeth Biopharma** to develop carrier formulations for delivery of recombinant human Bone Morphogenetic Protein-2 (rhBMP) for general orthopaedic applications. The company also received FDA 510(k) clearance to market Cap3, a synthetic, biocompatible bone graft substitute intended for use in bone void filler applications in the spine, pelvis and extremities.

Through its alliance with **Regeneration Technologies** (RTI), Exactech distributes flowable and moldable bone pastes (DBM and a gel carrier) for non-spinal applications. Exactech and Regeneration Technologies will also develop biological materials for use in the repair of damaged or diseased cartilage.

Exactech entered into the spine graft market with the first implantation of Optecure, a DBM in a synthetic bioabsorbable polymer carrier. Exactech will market OpteMx, a TCP/HA-based synthetic bone graft extender designed for spinal and general orthopaedic applications that is licensed under an exclusive U.S. distribution agreement with **Biomatlante**.

In Europe, **Fidia** markets Hyalograft C, a cartilage substitute made of autologous chondrocytes delivered on a biocompatible 3D matrix composed of Hyaff, a derivative of hyaluronic acid. The product is indicated for use in the treatment of defects of the femoral condyle, patella and tibial plateau.

Genzyme Biosurgery's orthobiologic initiatives began with the 1995 introduction of Carticel (autologous cultured chondrocytes), a biologic implant for the repair of full thickness defects in the articular cartilage of the knee. Through the Carticel procedure, surgeons biopsy healthy knee cartilage cells arthroscopically and send them to Genzyme, where they are grown *ex vivo*. The surgeon then reimplants the cells into knee defects and covers them with a periosteal flap. Carticel is cleared for use in the U.S. and Europe. **US**

Bioservices provides Carticel C Care, a comprehensive clinical case support and health insurance authorization services program for patients and physicians.

Genzyme's Carticel II, intended to simplify chondrocyte delivery and reduce surgical invasiveness, is undergoing preclinical trials. Benefits over the current Carticel product include the ability to be implanted in an arthroscopic procedure and the elimination of the periosteum which makes open knee surgery necessary. The company also has several early stage development programs that are exploring the use of advanced biomaterials, small molecules and stem cells for both OA and cartilage repair.

With its acquisition of **Verigen** in 2005, Genzyme has access to cell culture facilities in Europe and Australia to support sales in those regions, where Verigen's proprietary Matrix-induced Autologous Chondrocyte Implantation (MACI) product for cartilage repair is currently sold. Genzyme anticipates U.S. clinical trials of the procedure in early 2006.

Further, Genzyme has access to Verigen's ACI technique, which has been used successfully in the treatment of numerous patients in Europe and Asia Pacific. The technique obviates the need for periosteal graft (often used to cover the chondral defect after implantation of the cells), using instead a highly purified resorbable porcine collagen I/III membrane (seeded with cells) to cover the defect.

GMReis markets (outside the U.S.) Sponjosa, a ß-TCP bone graft material; New Osteo calcium sulfate; and SEFC, a separator and ultraconcentrator of growth factors. The company is developing tissue engineering products for orthopaedic and spine applications, such as autologous chondrocyte transplantation.

Inoteb manufactures a bone graft substitute made of natural coral, commercialized under the name Biocoral for use in orthopaedics, neurosurgery, maxillofacial surgery and oral surgery. Research & development projects at the company include osteoporosis fracture treatment and prevention, growth factors and an autologous biological glue for surgery.

Insmed has developed SomatoKine, an insulin-like growth factor shown to stimulate muscle and bone growth. Data from a Phase II clinical feasibility study using SomatoKine to treat severely osteoporotic

patients recovering from hip fracture surgery suggest that the factor has the potential to amplify bone metabolism and reverse the loss of bone mineral density, and that these effects may be sustained for up to four months.

Integra LifeSciences develops and manufactures implants and other medical devices used primarily for the treatment of defects, diseases and injuries involving soft tissue and bone, with most products built on the company's expertise in absorbable collagen products. The company supplies its Absorbable Collagen Sponges to Medtronic Sofamor Danek for use with its rhBMP-2, which is used in both its InFuse Bone Graft for spinal fusion applications and InductOs Bone Graft used in the treatment of acute long-bone fractures requiring open surgical management. Additional matrices for various applications are under development by Integra.

Integra continues to develop new classes of absorbable polycarbonates (through the polymerization of tyrosine) that enhance the rate and quality of healing and tissue regeneration with synthetic biodegradable scaffolds that support cell attachment and growth. To date, the company has not commercialized any medical device based on these materials.

IsoTis OrthoBiologics sold its wound management activities and now focuses solely on orthobiologic products, which include Accell Total Bone Matrix (TBM), reportedly the first pre-formed 100 percent DBM in the orthopaedic industry along with FDA-cleared Connexus with 70 percent DBM by weight; FDA-cleared DynaGraft II Putty and Gel (DBM in a reverse phase medium); OrthoBlast II DBM and cancellous bone in putty and paste; and OsSatura TCP synthetic bone substitute which is FDA-cleared and certified under the CE Mark. Through a three-year non-exclusive agreement, **Lifetek** and **Endoplant** (subsidiaries of **PLUS Orthopedics**) distribute DynaGraft II and OrthoBlast worldwide.

Through a commercial alliance, IsoTis and Teknimed jointly develop synthetic-based products (i.e., OsSatura) for use in orthopaedic, spine and trauma surgery. Teknimed develops and manufactures calcium phosphates and other biomaterial-based products.

Isto Technologies intends to develop products for the repair, regeneration and restoration of function to injured or worn-out cartilage in joints. The company's tissue-engineered Neocartilage (cultured from human chondrocytes) has demonstrated *in vitro* biochemical and histological properties very similar to normal articular cartilage. Unlike other chondrocyte technologies, Neocartilage does not require the use of scaffold materials to form 3D tissue.

Financing that included funding from Zimmer, Isto's development partner, will help progress Isto's cartilage repair products to human clinical trials. Neocartilage is currently in research for spinal indications and in preclinicals for use in knee injuries. Isto plans to introduce a first generation Neocartilage product in 2005 or 2006. Additional studies of Neocartilage will be used to evaluate the technology's ability to repair cartilage lesions in sheep, allowing for *in vivo* evaluation of the neocartilage allograft.

Isto and Zimmer will collaborate to develop and commercialize Neocartilage for surgical repair of articular cartilage defects and potentially for the regeneration of articular surfaces lost to OA. Isto will also develop an osteochondral allograft.

Japan Tissue Engineering (J-TEC) is conducting a five-hospital clinical trial aimed at treating patients with damaged elbow or knee joints as a result of accidents, sports activities or disease. The treatment involves a one-month cultivation in collagen of a sample of a patient's own healthy cartilage. The sample is then implanted into the damaged joint and covered with periosteum. The surrounding area is expected to regain hardness within two years. Researchers tested the technique on 80 patients in 1996, and stated that "about 90%" of those involved are satisfied with the process. The company hopes to obtain regulatory clearance for the technique in 2007.

In orthobiologics, Johnson & Johnson markets Restore, a soft tissue implant derived from porcine small intestine submucosa used as a soft tissue attachment device in shoulder applications. Restore, shown to spur bone and tissue growth, is cleared for use in all tendons of the rotator cuff and will be investigated for its use in other soft tissue and spinal repair. DePuy also markets Cellect, a minimally invasive system for iliac crest bone graft harvesting; Etex's α-BSM; Conduit TCP; **LifeNet**'s VertiGraft tissue-engineered allograft implants for spine surgery; and Optium putty and gel DBM (through agreements with **Osteotech**

and LifeNet). As a result of acquiring all of the assets of **Orquest**, DePuy has distribution rights to CE-marked/FDA-cleared Healos Bone Graft Material, a resorbable HA-coated, porous, mineralized collagen fiber matrix used with autologous bone marrow. DePuy also licenses a broad BMP technology portfolio (including rhGDF-5 and its derivatives) from **Biopharm** on an exclusive worldwide basis for musculoskeletal indications. The company has completed enrollment in its Healos/rhGDF-5 spine fusion pilot study, and expects to enter a pivotal clinical study in the U.S. in 2006.

The Biopharm license includes current and future applications in musculoskeletal tissue repair (excluding dental and maxillofacial) with additional rights in other fields. The companies are investigating the use of BMP in such areas as bone grafting, cartilage regeneration and meniscal repair, with further collaboration to combine the rhGDF-5 growth factor or derivatives with proprietary bio-engineered scaffolds.

A variety of other research initiatives are underway at Johnson & Johnson, including cell-, matrix- and bioactive factor-based technologies. DePuy has already begun clinical studies of Remenisc, an off-the-shelf, resorbable meniscal repair device. In addition, the company intends to initiate clinical studies of its Cartilage Autograft Implantation System (CAIS), which integrates the patient's own cells in a single procedure, with an intraoperative device. This approach builds on the success already established by the company's Cellect Bone Grafting System, which is FDA-cleared for the intraoperative concentration of marrow-derived stem cells.

Kasios specializes in the development, manufacture and sale of synthetic bone substitutes for use in orthopaedics and dental surgery. The company's line includes Jectos calcium phosphate, TCH biphasic ceramic (75% hydroxyapatite and 25% tricalcium phosphate), and FDA-cleared Kasios TCP, a macroporous synthetic bone substitute made of 99.9% tricalcium phosphate. All products are certified under the CE Mark.

Kensey Nash manufactures medical-grade porous constructs comprising synthetic and natural polymers in a variety of configurations. The company's polymer technology platform includes a porous tissue matrix technology that allows it to create porous implants that support cell growth, tissue regeneration and the delivery of biologics, growth factors, etc. Kensey's research in this area includes applications for articular

cartilage regeneration and bone growth scaffolds for spinal and trauma indications and delivery of drugs and growth factors.

Kensey's expertise also includes ceramics, primarily calcium phosphates, which can be compounded with resorbable polymers for orthopaedic applications. The company is working with numerous orthopaedic companies to incorporate its ceramic/polymer technologies into existing products or to develop new products. Kensey will advance development of rotator cuff repair and bone graft containment products based on its BioBlanket proprietary resorbable collagen sheet technology, which is FDA-cleared for use as a patch for reinforcement and repair of ruptured or damaged soft tissues, including rotator cuff procedures.

In bone graft materials, Kensey Nash is developing substitutes derived from collagen, synthetic polymers, ceramics and composite biomaterials. Kensey and Orthovita have collaborated to develop bone graft products, with Kensey Nash manufacturing products combining Orthovita's Vitoss with its biomaterials. The first of these products – Vitoss Scaffold FOAM FLOW – entered the U.S. market in 2004. Vitoss FOAM Pack, the latest addition to the line, received FDA clearance for use in the spine, pelvis and extremities.

Keraplast Technologies has an extensive portfolio of keratin-related patents covering such diverse applications as wound healing, bone regeneration, tissue scaffolds and protein coatings for medical devices. The company entered into a collaborative agreement with **Keratec** to produce wound healing and orthopaedic products.

In late 2005, **Kobayashi Pharmaceutical** plans to launch Cerapaste, a bioactive bone cement developed by **NGK Spark Plug**. Japan MDM will collaborate on sales.

Kuros Biosurgery will develop two major families of products – one for bone support and fixation (e.g. for vertebroplasty) and the other for bone repair and regeneration as a bone graft substitute in orthopaedic, CMF and dental use. Beyond vertebroplasty, Kuros will seek to develop second generation products designed to repair fractured vertebral bone and regenerate functional bone. The company's Synthetic Repair

Tissue (SRT) technology involves materials that transition from liquid to solid, allowing them to be fully integrated through MIS approaches. The materials can be made with various combinations of strength, elasticity, resorption and bio-functionality. SRT has also been used to make synthetic mimics of natural matrices such as fibrin and collagen.

Kuros initiated a prospective study in Switzerland to evaluate its *in situ* polymerizing bone graft substitute as an adjunct to open reduction with standard fixation in patients with distal radial compression fractures.

Kuros Biosurgery and Baxter are engaged in a broad research and development collaboration for the localized, sustained delivery of growth factors from a fibrin matrix for tissue regeneration. Baxter will receive rights to exclusively develop and market Kuros' fibrin-based growth-factor delivery technologies in skin and orthopaedic indications.

LAGeT (light activated gene transduction) is focused on developing gene therapeutic approaches for musculoskeletal diseases, including articular cartilage defects. Company researchers hope to further develop a technology that uses ultraviolet laser light to induce the expression of a therapeutic gene known to stimulate regrowth of articular cartilage. The process has worked successfully in cellular experiments and in bone grafting in mice. LAGeT plans to conduct animal experiments involving cartilage growth and spinal fusion to develop the evidence necessary for approval of human clinical trials.

A research team from **Lausanne University** has developed a synthetic polymer-ceramic bone replacement material that could have application in cases of tumor/deformity filling, trauma, etc. In laboratory tests, bone cells grew into the material within three to four weeks and proceeded to multiply. The material may be able to fulfill a structural role while bone cells proliferate into its porous inner section.

Preclinical studies suggest that **LifeCell**'s cell-free tissue matrix can remodel tendon and ligament tissues. Wright Medical holds exclusive U.S. distribution rights to GraftJacket, an acellular tissue matrix for orthopaedic applications provided by LifeCell, as does Stryker for AlloCraft, a bone grafting product that combines LifeCell's proprietary tissue processing technology with DBM.

LifeCell continues to evaluate orthopaedic applications of its tissue matrix technology, with preclinicals underway to investigate the ability of acellular tissue matrices to remodel into various orthopaedic tissues. The company intends to conduct additional studies investigating the potential of its tissue products to remodel into such orthopaedic tissues as tendon, ligament, cartilage, meniscus and bone; and is completing process development of applying its matrix technology to allograft tendons for use in ACL repair procedures.

LifeNet introduced Allowash XG, a process for cleaning and disinfecting donated bone. The procedure includes donor screening, a "more robust" processing regimen and a terminal sterilization step at low temperatures to produce sterile tissue. LifeNet allografts to be treated with Allowash XG include MatriGraft, FlexiGraft, ReadiGraft and VertiGraft.

Medartis has CE Mark approval and FDA 510(k) clearance for its synthetic bone void fillers – Synthacer, a non-resorbable HA ceramic and Syntricer, a resorbable TCP. Both are available in blocks, cylinders and customizable configurations for general orthopaedic applications. The Medartis process reportedly allows for the customization and control of pore structure, pore size and continuous connectivity. Medartis and Musculoskeletal Transplant Foundation work together to design, develop and manufacture ceramic constructs and other orthopaedic products, with Musculoskeletal Transplant Foundation marketing and distributing them worldwide (excluding Austria, Germany, Liechtenstein and Switzerland).

Medicrea markets its CE Mark approved and FDA-cleared bone substitute outside the U.S. Osmosys, available in granules and sticks, is comprised of 60% HAP and 40% TCP.

Medtronic markets a wide variety of orthobiologic products, including MasterGraft, an HA/TCP bone graft substitute for use in filling bony voids of the extremities, pelvis and spine; the Magellan Autologous Platelet Separator, which separates platelet-rich plasma containing growth factors; a variety of structural and non-structural allograft products and formulations of Osteofil injectable DBM/gel bone paste, sourced from Regeneration Technologies..

Medtronic Sofamor Danek's key orthobiologic product is InFuse Bone Graft (recombinant human Bone Morphogenetic Protein-2/absorbable collagen sponge). InFuse has regulatory clearance in the U.S. and Canada for treatment of certain types of spinal degenerative disc disease. The BMP is marketed for use with the company's LT-CAGE and Inter Fix interbody fusion devices.

RhBMP-2 is also FDA-cleared for use in the treatment of adult acute, open fractures of the tibial shaft. (The product had already been cleared in Europe.) Medtronic Sofamor Danek has worldwide exclusive rights to market rhBMP-2 in the U.S., Canada, Australia, Latin America and other countries for spine, orthopaedic and trauma indications and in Japan and Asia for use in orthopaedic surgery. In Europe, MSD markets InductOs Bone Graft (known as InFuse in the U.S.) for use with certain sizes of the LT-CAGE for adult single-level lumbar spinal fusion.

Through collaboration with **TEI Biosciences**, Medtronic Sofamor Danek and TEI intend to develop TEI's collagen scaffolds, signaling molecules and cells for neurosurgical and orthopaedic systems that closely mimic those needing replacement. Medtronic Sofamor Danek owns the rights to use **Emory University**'s LIM Mineralization Protein-1 (LMP-1) gene in spinal fusion applications. Data from animal studies of BMP-2 and LMP found that the molecules have a therapeutic effect on disc health and hydration.

Mesoblast received approval to begin the first human orthopaedic trial of its specialized adult stem cell technology, known as Mesenchymal Precursor Cells. The pilot trial will treat up to ten patients suffering from long bone nonunion fractures. The company also commenced pre-clinical trials of its proprietary universal adult stem cells for treatment of long bone fractures and for spinal fusion. Initial results are expected in three months.

Millenium Biologix's proprietary synthetic biomaterials technologies include Skelite synthetic resorbable biomaterial (calcium phosphate) for the repair of osseous defects in the extremities, spine and pelvis (cleared in the U.S., Canada and Europe); and porous 3D Skelite Synthetic Scaffolds for large defect repairs. Spinal Solutions carries Skelite in Texas and Oklahoma, and EBI is a non-exclusive U.S. distributor as well. In Europe, Millenium's own sales team and agency partners market Skelite in select countries.

The company submitted a 510(k) to FDA to market its Microporous Skelite Resorbable Cement Restrictor.

Enhanced versions of Skelite under development include CartiGraft, through which autologous cartilage constructs are integrated with Skelite scaffolds for use in the treatment of osteochondral defects.

Implant testing is underway of Skelite treated with Millenium's BCSP (Bone and Cartilage Stimulating Peptides), a proprietary range of peptides that have shown specific growth promoting activity in bone and cartilage. BCSP technologies under development include Peptos, a synthetic bone growth factor bound to a Skelite scaffold for delivery to the surgical site and SOAP (Systemic Osteoporosis and OsteoArthritis Peptides) for the systemic treatment of bone diseases. Preclinical studies of Peptos have been completed, and the company has filed an Investigational Device Exemption for the product. SOAP remains in development.

Millenium received clearance under the CE Mark for Primacoll synthetic bone graft substitute and launched the product in Europe through its own distributors. A Canadian sales and distribution agreement was signed with **Joint Solutions Alliance**, to initially focus on Skelite in spine, neuro and trauma applications. Primacoll features Skelite coated with a synthetic fragment of human collagen to improve healing.

Millenium has also developed cell culturing and tissue engineering biosystems, including ACTES (Autologous Clinical Tissue Engineering System), which will make possible the culturing of autologous chondrocytes in hospitals and clinics. Development of ACTES-C (Cartilage Tissue Engineering) is at an advanced stage, with beta-test site systems scheduled for delivery in 2005. An exclusive license agreement with the **Massachusetts Institute of Technology** will help Millenium to obtain a larger number of cells reportedly retaining a "superior capacity" to produce cartilage tissue. Millenium plans to also produce ACTES products for bone and other cell/tissue applications.

Millenium and **Procter & Gamble Pharmaceuticals** are engaged in a research agreement whereby the latter will evaluate therapeutic potentials of Millenium's proprietary synthetic BCSPs to treat diseases of bone and cartilage. In addition, Millenium and Baxter HealthCare are collaborating to study the use of

Baxter's Tisseel fibrin sealant for delivery of BCSPs with or without Skelite in an animal fracture model. Results indicate that Tisseel could be formulated to produce both an injectable growth factor delivery for fracture repair and a malleable bone putty when combined with Skelite.

Musculoskeletal Transplant Foundation, the world's largest tissue bank, procures and distributes a variety of allograft tissue including base tissue, structural grafts, osteochondral and meniscal allografts, bone-tendon-bone constructs, allograft tendons, DBX Demineralized Bone Matrix and AFT bone void filler (both FDA-cleared), a patented form of human allograft tissue that combines demineralized bone with a natural carrier (an aseptic solution containing hyaluronan sourced from **Lifecore Biomedical**); and structural spinal allografts distributed in the U.S. by **Synthes Spine**.

Musculoskeletal Transplant Foundation acquired assets related to American Red Cross Transplantation Services' allograft tissue banking operations, and signed a collaborative development agreement with Bone Biologics to provide customized tissue forms to support the delivery of a molecule called UCB (University of California Bone). UCB works synergistically with BMPs to form more bone than is typically formed with BMPs alone and potentially has fewer side effects than BMPs.

Musculoskeletal Transplant Foundation's other relationships include one with Stryker, through which the companies will combine allograft with Stryker's OP-1 BMP; a development, distribution and marketing agreement with Spineology for co-development of a delivery system for Musculoskeletal Transplant Foundation's allograft bone with Spineology's OptiMesh bone graft containment system; and an exclusive worldwide product license agreement with Medartis covering certain ceramic-based products and technologies. Musculoskeletal Transplant Foundation also made an equity investment in Vertebron and the two will partner to develop, co-market and distribute specified bone grafts in addition to synthetic constructs within certain international markets. **Northwest Tissue** Center provides the Foundation with bone to be processed into machined grafts and demineralized bone pastes, putties and gels, which are promoted in healthcare facilities by Synthes. Finally, through an exclusive agreement with **Orthocon**, Musculoskeletal Transplant Foundation has rights to novel products including those that stimulate new bone growth. Products are based on allograft and non-allograft formulations and have application in a variety of orthopaedic areas (e.g. spine, trauma, sports medicine, joint replacement).

In a mouse study, researchers from the **University of Rochester Medical Center** achieved the transformation of dead bone from a transplanted skeletal graft into living tissue. Scientists modified a harmless virus to carry genes that create 2 key proteins in living bone, then painted a freeze-dried virus-imbued paste onto bone graft. Tests confirmed that the virus permeated tissue around dead bone and "turned on" the genes. The mouse body then proceeded to treat the implanted bone as if it were its own tissue. The Musculoskeletal Transplant Foundation has pledged to continue support of the project.

NeuColl has been acquired by Angiotech Pharmaceuticals. NeuColl's product platform comprises Collagraft and Neugraft Bone Graft Matrices – collagen-based synthetic bone graft substitute products that combine a composite of purified fibrillar collagen with HA and calcium phosphate. The products are cleared for use in treatment of acute long bone fractures, traumatic osseous defects, bony voids or gaps that are not intrinsic to the stability of the bony structure. While Zimmer holds distribution rights for both products in the U.S., Japan and other countries, NeuColl relies on independent agents for distribution of the products in Europe.

Nexa Orthopedics received FDA 510(k) clearance for Futura Biomedical's OsteoCure Resorbable Bead and OsteoCure Injectable Graft kits. (Nexa acquired Futura in 2005.) OsteoCure is intended to be placed into bone voids or gaps; or molded into solid pellets that are packed into bone voids or gaps that are not intrinsic to the stability of the bony structure of the skeletal system.

NovaBone's synthetic bone graft materials business features NovaBone C/M and NovaBone resorbable calcium phosphosilicate granules derived from Bioglass. Cleared in the U.S. and the European Union, NovaBone products have been used in more than 700,000 cases – orthopaedic defect filling for NovaBone and craniomaxillofacial grafting for NovaBone C/M. Results from an independent clinical study of 20 elective, single-incision primary lumbar fusion patients demonstrated that NovaBone stimulated new bone formation on an "equivalent basis" compared to BMP-2 when each was used in a composite of either NovaBone + bone marrow + local bone + BMP-2 and NovaBone + bone marrow + local bone.

NuVasive entered into a supply agreement with the **Blood and Tissue Center of Central Texas**. The Center will process, package and supply NuVasive with human allograft bone tissue for transplantation for a three-year term.

Olympus Biomaterial focuses on bone tissue engineering and artificial bone replacement materials. The company has been a leading provider of bone graft substitutes in Japan since 1999, through sale of its OS-ferion ß-TCP bone replacement. The company acquired the bone replacement material business of Sumitomo in 2005, and intends to dedicate future resources to articular cartilage tissue engineering and biomaterials for dental applications.

Through a joint venture partnership**, Ortec** is studying how the properties of its proprietary collagen biomaterial scaffold may work with **Hapto Biotech**'s Haptide technology, which uses proprietary synthetic peptides that mimic cell attachment to fibrin. The companies are assessing the safety and efficacy of a non-cellular peptide-based collagen biomaterial in promoting attraction and attachment of healthy cells *in vivo* in tissue regeneration, and will seek licensing opportunities for co-development and commercialization of the product for indications including reconstructive orthopaedics. An animal study showed that Ortec's scaffold, modified by attachment of Haptides, had a higher cell binding potential than standard, untreated collagen.

Orthocon's development activities center on its proprietary Syntinate platform, comprising natural and synthetic orthobiologic compounds with specific absorption and release attributes for intraoperative drug delivery. The company has licensed its first four products and received FDA clearance for its Orthostat Hemostatic Bone Putty, a moldable, absorbable calcium stearate-based mixture intended for use in the management of bleeding from the cut surface of bone.

Orthogen's orthobiologics franchise includes Arthromatrix, a procedure for growing cartilage cells *in vitro* and transplanting them. Arthrex distributes Arthromatrix outside the U.S.. Orthogen has also developed a patented, time-release calcium sulfate-based composite for bone regeneration and repair and expects to initiate animal studies of the material. Further, the company is working with **Harvard** researchers

on the development of a technology that can grow cartilage tissue from adult stem cells, which has yielded quality cartilage in animal study.

OrthoLogic owns all assets and intellectual property of **Chrysalis BioTechnology**, covering exclusive rights to proprietary technology and intellectual property in developing synthetic peptide-based therapeutics for a variety of indications. OrthoLogic's lead product is Chrysalin, a synthetic thrombin peptide, which has been shown to accelerate repair of articular cartilage defects and healing in animal fracture models.

OrthoLogic completed enrollment (502 patients in 27 centers) in a pivotal U.S. Phase 3 human clinical trial evaluating Chrysalin in treatment of unstable distal radius fractures. Trial results are expected in the first half of 2006. A Phase 2b dose-ranging human clinical trial is underway for this same indication, to support a filing with FDA that could come by the end of 2006.

OrthoLogic is collecting data from a pilot Phase 1/2 clinical trial of Chrysalin in spinal fusion, for which results are expected in 2005. The company continued preclinical activities on potential Chrysalin products for cartilage defect repair and hopes to submit an Investigational New Drug application for a cartilage defect repair indication and begin a human clinical trial in 2005. Further, the company has initiated its first preclinical study in tendon repair.

Orthomed markets Sobio Biphasic Bone Substitute (tricalcium phosphate and hydroxyapatite) globally in blocks, granules, cylinders, etc.

Orthopeutics focuses on nonsurgical treatment for the repair of intervertebral discs, in particular the use of injectable, collagen crosslinking reagents to stabilize intervertebral joint motion without adversely affecting range of motion. The company's Nonsurgical EXogenous crosslink Therapy (NEXT) has been shown to improve disc durability, while also doubling fluid flow to the central disc, thus providing an increased supply of nutrients to the disc for reparation.

Orthovita's orthobiologic franchise includes Vitoss, a resorbable, highly porous, β-TCP bone void filler; Vitagel, a hemostatic agent; and Cortoss, an injectable, immediately load bearing, bone bonding composite. In 2004, the company terminated a development program relating to Rhakoss, a proprietary Orthobone bioactive composite-based technology that had been under development as a synthetic bioactive bone-bonding, load-bearing pre-formed spinal implant product.

Orthovita has introduced an array of Vitoss Scaffold products in Australia, Europe and the U.S. and will work to obtain approval to market the products in Japan. The Vitoss Foam product line received certification under the CE Mark in 2005.

Orthovita's Cortoss is cleared for marketing in both Australia and Europe for use in screw augmentation and vertebral augmentation procedures, with post-marketing human clinical studies completed for its use in hip compression screw augmentation in Europe. In the U.S., Orthovita made progress in its clinical trials with Cortoss for the treatment of vertebral compression fractures using the vertebroplasty and kyphoplasty techniques, as well as in the treatment of anterior skull base defects. In 2004, FDA granted the company clearance to amend its pivotal clinical trial protocol such that Cortoss would be compared directly with PMMA bone cement. The study marks the first of its kind and will enroll approximately 300 patients, assessing the ability of Cortoss to provide pain relief and improvement in function by restoring weight-bearing strength and stability to the fractured vertebra.

Orthovita markets additional products that address delivery of biomaterials (the Aliquot Microdelivery System) as well as products that allow for the combination of Vitoss with bone marrow aspirate (e.g. the Imbibe Bone Marrow Aspirate Syringe). The company's strategic alliance with Kensey Nash has resulted in a number of new products, including Vitoss Scaffold Foam Flow ultra-porous, flowable material, and Vitoss Foam Pack, a compression-resistant ultra-porous structure that offers putty-like handling. The product is FDA-cleared for use in the spine, pelvis and extremities. Orthovita also has a supply agreement with BioMimetic Therapeutics, through which BioMimetic uses its rhPDGF in combination with Orthovita's Vitomatrix particulate synthetic (calcium phosphate) scaffold biomaterial. Orthovita supplies Vitomatrix to BioMimetic for its clinical and commercial use in conjunction with rhPDGF. BioMimetic will market and sell the combined product (upon approval) in the dental, periodontal, oral and CMF bone

grafting markets. Under a North American sales and distribution agreement, Orthovita markets Angiotech Pharmaceuticals' Vitagel and the Cellpaker collection system for use in spine and orthopaedic surgery.

Osiris has developed and patented a manufacturing process for the expansion of human mesenchymal stem cells (hMSCs), which could be used in the regeneration and functional restoration of bone and soft tissue. The company's Chondrogen, an injectable preparation of MSCs, will be administered to the knee joint after partial meniscectomy for meniscal injury in planned clinical trials; patient enrollment has commenced for a Phase I/II study of this indication. In preclinicals, allogeneic MSCs delivered intra-articularly to the knee joint stimulated the regeneration of lost meniscal tissue. The company commenced distribution of allogeneic bone matrix containing viable stem cells, indicated for the repair, replacement and reconstruction of bone defects, which it will distribute directly under the product name of Osteocel. Blackstone Medical will distribute Osteocel to spine surgeons as the Trinity brand.

Ossacur seeks to enter the U.S. market with its FDA-cleared OSSAPLAST beta-tricalcium phosphate ceramic implant for the filling and reconstruction of bone defects. The company retained **Hatch Medical**, a medical device incubator and technology brokerage firm, to identify and secure a U.S. distributor for the device.

Ossacur focuses on the development and production of resorbable implants based on native collagen. The company's products include Colloss, a resorbable implant for the filling of bone defects, and Targobone, which comprises Colloss plus antibiotic. Both are distributed by Biomet.

OssTech is an early-stage medical device company developing novel synthetic bone substitute materials. The company's core technology is based on OsteONE, a silica-calcium phosphate nanocomposite material for orthopaedic, spinal and maxillofacial applications.

OsteoBiologics received FDA clearance, Canadian regulatory clearance and certification under the CE Mark for a variety of bone graft products based on its patented PolyGraft technology, which combines polylactide-co-glycolide, calcium sulfate and polyglycolide fibers in granules, cubes, blocks and pre-formed cylinders. OsteoBiologics is also developing the resorbable IMMIX-CB, a multi-phase (carti-

lage/bone) implant that can reportedly support repair in both weight bearing and non-weight bearing applications. In a preclinical animal study of osteochondral defect repair, the company's multiphasic porous scaffolds provided a structurally sound conduit to support tissue ingrowth during joint use. Nexa Orthopedics has exclusive rights for U.S. distribution of certain of OsteoBiologics' hand, foot and ankle products under Nexa's OsteoCure brand. The companies will also co-develop extremity reconstruction products. OsteoBiologics also signed an exclusive agreement whereby ConMed Linvatec will distribute the company's cartilage and bone repair products outside the U.S. for use in sports medicine and arthroscopy procedures.

OsteoGenesis intends to commercialize technology that combines mesenchymal stem cells with appropriate scaffolds. Although it will initially focus on the oral maxillofacial field, OsteoGenesis' injectable bone regenerating material has application across all musculoskeletal areas.

Osteogenetics owns a technology platform for the development and production of what it terms "second generation" pharmaceuticals based on BMPs and transforming growth factors. The company believes that its BMP technologies may induce bone formation of qualitatively and quantitatively better bone substance than allowed by existing materials. Osteogenetics expects to produce its second generation BMPs, characterize their properties and create a composite with suitable matrix materials, with efficacy to be established in animal studies. No notable progress has been made for the company over the past 12 months.

Osteotech is one of the world's largest processors and developers of allograft bone tissue forms, including Grafton DBM and base tissue. The company processes tissue procured by its clients, such as LifeNet, which also distribute Grafton and other allograft products to the end user market. Outside the U.S., Osteotech's **OST Developpement** subsidiary processes, markets and distributes OsteoPure Femoral head bone tissue outside the U.S. in addition to bovine bone tissue products (Lubboc and Laddec lines).

Osteotech's Grafton line of products includes gels, putties, "pressed fiber" forms of DBM, DBM with cortical cubes, etc. The Grafton family includes Orthoblend in two formulations; one containing demineralized bone fibers with cancellous chips for large defects, and one containing demineralized bone fibers and crushed cancellous chips for smaller defects. Both products obviate the need to mix ingredients dur-

ing surgery. Osteotech is seeking FDA clearance for its Grafton Plus with a starch carrier and remains in discussions with FDA as to the regulatory status of glycerol-based Grafton, which FDA had originally indicated was human tissue and hence, not subject to regulation as a medical device. Osteotech and all other manufacturers of DBM products have been notified that FDA will classify DBM products as devices, therefore requiring FDA 510(k) clearance by mid-November 2005.

The Graftech Lordotic Cervical Spacer is Osteotech's latest addition to its Bio-Implant line. The device, comprising dense cancellous tissue, features 7º of lordosis and utilizes instrumentation already available to surgeons. Osteotech also introduced the Xpanse Bone Insert and the GraftCage TLX vertebral body replacement devices. Xpanse incorporates demineralized bone fiber and cancellous chips to yield a tissue graft that is osteoinductive, osteoconductive and osteoconforming. GraftCage, manufactured from Invibio's PEEK-OPTIMA polymer, features a large opening for insertion of fusion-enhancing materials (such as Xpanse). GraftCage is expected to receive FDA clearance in late 2005.

Osteotech signed an agreement with DePuy and LifeNet for the processing and distribution of a private label DBM carrier product in the U.S., with LifeNet supplying bone, Osteotech processing it and DePuy promoting the product. DePuy also serves as the exclusive sales agent for Grafton DBM grafts in Germany, Switzerland and the U.K. Osteotech also distributes Graftech Bio-Implant spacers and ramps for spinal fusion applications.

In early 2004, Osteotech entered into a 5-year agreement with Smith & Nephew for the processing and distribution of a private label DBM for non-spinal orthopaedic applications. Products to be launched through the agreement include gel, putty, paste, flex and demineralized cancellous crunch forms of allograft.

Osteotech has licensed a polymer from **Rutgers University** for use as part of its Plexus technology under development. Plexus comprises a range of bone and polymer composites that remodel into a patient's host bone while upholding the strength requirements of weight-bearing applications.

As part of its intention to diversify global donor sources, Osteotech anticipates that termination of its business relationship with the Musculoskeletal Transplant Foundation will occur at the end of 2008.

Pegasus Biologics manufactures and sterilizes collagen-based bioimplants for use in soft tissue reinforcement specifically for orthopaedics, sports medicine, neurosurgical and spine applications. Studies of the company's FDA 510(k)-cleared OrthADAPT Bioimplant indicate that the scaffold demonstrated excellent biocompatibility and tissue regenerating properties. The Pegasus UltiFIX crosslinking technology allows full biocompatibility, while the UltiSTER technology sterilizes the bioimplant without chemicals or radiation.

Progentix' platform technology centers on a stand-alone, automated, closed bioreactor system that can expand bone marrow derived adult mesenchymal stem cells. The company focuses on the use of these cells in bone regeneration and has also developed osteoinductive synthetic materials that can be used as bone grafts or tissue scaffolds for the regeneration, reconstruction or augmentation of skeletal defects. Progentix seeks partners for further development of its stem cell technology and commercialization of its bone graft portfolio.

pSivida signed an agreement with **Pure-Tech Development** to investigate out-licensing opportunities for its BioSilicon (nano-structured porous elemental silicon) technology with an emphasis on wound management, tissue engineering and orthopaedics. For the latter, a range of BioSilicon and composite devices are under consideration, e.g. screws, braces, pins and staples for reconstructive surgery, or as a device coating. BioSilicon has demonstrated the ability to stimulate osteoblasts and promote bone mineralization *in vitro*, and has the osteoinductive characteristics of established orthopaedic materials.

ReGen Biologics has developed several proprietary forms of collagen as well as tissue-matrix engineering processes to fabricate resorbable and self-expanding matrices to guide natural tissue regeneration. The company's lead orthobiologic product, the Collagen Meniscal Implant (CMI), is a synthetic bovine cartilage/collagen template that has demonstrated marked postoperative improvement and regeneration of cartilage. The company regained from Zimmer its rights to exclusively market and distribute CMI worldwide, and has a wholly-owned subsidiary in Switzerland to market the device in Europe. CMI is cleared

for marketing in Europe, Australia and certain other countries. In the U.S., ReGen expects to complete its PMA submission in the second half of 2005. Early research and development with the company's core technology includes programs in spine and articular cartilage.

Regeneration Technologies processes and sterilizes human tissue into a wide variety of allograft implants for orthopaedic applications, including bone, cartilage, tendons and ligaments. The company uses its own salesforce for distribution of some of its conventional allografts for oral and maxillofacial surgeries, while Exactech and Medtronic Sofamor Danek distribute the company's allografts and bone pastes for orthopaedic and spinal applications, respectively. Having terminated a distribution agreement with Stryker Endoscopy, Regeneration Technologies now uses a direct sales force for its sterilized sports medicine allografts.

In 2005, Regeneration Technologies signed a five-year agreement with **Southeast Tissue Alliance** for the recovery of human donated tissue (e.g. bone, tendons, ligaments). The company will test and shape recovered tissues into final implant form, which will be sterilized through the BioCleanse process before use in orthopaedic and spinal surgeries. Since mid-2004, Regeneration Technologies has distributed approximately 540,000 implants sterilized by BioCleanse with no incidence of infection reported.

Regeneration Technologies obtained FDA 510(k) clearance for its DBM paste products (e.g. Regenafil and Regenafil RT, Optefil and Optefil RT, Osteofil and Osteofil RT, RTI Allograft Paste, syringes, etc.); the xenograft Sterling Interference Screw ST, intended for use in arthroscopic or open anterior and/or posterior cruciate ligament reconstruction; and for Sterling Cancellous Chips and Cubes, treated with BioCleanse and intended as a bone void filler following surgery or traumatic injury. The company is currently pursuing 510(k) applications for additional xenograft implants for all product lines.

Regentis Biomaterials has developed a core technology platform called Gelrin for tissue regeneration. Gelrin is a biosynthetic hybrid hydrogel combining fibrin with polyethylene glycol. The material can be cross-linked either *in-situ* or *ex-vivo*, depending on the requirements of the application. The company plans to develop a product line beginning with GelrinCartilage, a matrix designed to trap autologous chondrogenic extract into a hydrogel network and stimulate cartilage formation by slow, passive diffusion

of chondrogenic factors. Other products in Regentis' pipeline include GelrinBone for use in craniomaxillofacial defects, bone voids caused by surgical interventions, long bone defects and fracture healing (non-weight bearing); and GelrinSpine, a matrix enhanced with TGF-beta for non-injurious bone formation and spinal fusion. The product may be placed in the fusion site using preformed constructs or by injection.

Replication Medical received funding from Abbott Spine which will help expand development of Replication's hydrogels and implants for spine care. The company's minimally invasive NeuDisc is a hydrogel-based spinal nucleus implant (based on Aquacryl proprietary polymer) that is inserted in a dehydrated, rolled-up wafer. When hydrated, the device locks in place, replacing the natural nucleus.

SaluMedica's lead technology is Salubria, a biostable, biomimetic hydrogel material that contains water in similar proportions to human tissue. Salubria has been shown to allow new cells to grow on it. The company received Canadian regulatory clearance and CE Mark approval for its SaluCartilage implant line, indicated for use in treatment of painful chondral or osteochondral defects of the articular cartilage surface. Arthrex distributes SaluCartilage on a limited basis in Europe, and in 2005 SaluMedica engaged in contract negotiations with reps in more than 20 countries to establish a network of independent distributors.

SBM specializes in resorbable surgical devices based on synthetic materials. The company's Bio1 implant, made from Biosorb synthetic ß-tricalcium phosphate, is FDA cleared for bone void filling and was reportedly the first such product approved in Europe under the CE Mark. SBM's materials, including Biosorb, Synatite (synthetic nonresorbable hydroxylapatite) and Duosorb (tricalcium phosphate ceramic and Poly DL lactic acid), form the basis for products such as the Tecma System for cervical interbody arthrodesis (Bio-Tecma resorbable and Tecma-Fx nonresorbable implants), the Otis Systems for high tibial osteotomy by internal addition, and Ligafix bioactive interference screws. All products are approved under the CE Mark.

Scient'x entered the bone graft substitute market with the U.S. launch of DyNoss, a cancellous bone void filler manufactured from a proprietary combination of HA/β-TCP.

Scil Biomedicals' expertise lies in tissue regeneration using a combination of recombinant proteins or peptides and a variety of biomaterials. Scil and Biopharm have developed MD05 for bone augmentation. MD05 brings together a bone growth-inducing protein rhGDF-5 coated onto a β-TCP carrier, with the company claiming that the product is the first calcium phosphate-based osteoinductive bone regeneration material developed for maxillofacial indications.

Products in research at Scil include ST01/ST02, calcium phosphate based osteoinductive bone regeneration materials for spinal fusion applications. A proof-of-concept study for ST01 revealed superior efficacy of the material to autologous bone in an *in vivo* preclinical study for posterolateral interbody spinal fusion. Scil has also performed preclinical efficacy testing of its ST03 product in animal models. ST03 consists of a chondrogenic protein, coated onto or incorporated into a biocompatible, biodegradable matrix. The material will likely have application in the treatment of osteochondral defects.

Skeletal Kinetics focuses on fracture repair and "mechanobiologic" solutions in bone repair. Its family of products includes resorbable Callos bone void filler (calcium phosphate-based) and a Callos formulation for craniomaxillofacial applications; Impact, a moldable, impactable material that may have application in augmenting fixation; Inject, an injectable paste; and OsteoVation CMF bone void filler, which may be used in the restoration or augmentation of bony contours of the craniofacial skeleton. All are FDA-cleared, and Callos is CE Marked. Skeletal Kinetics distributes Callos in the U.S. through a combined direct sales force, independent sales agents and distributors. Callos is also distributed internationally in certain countries in Europe and Asia-Pacific through a network of independent distributors. In the U.S., OsteoMed distributes OsteoVation as a private label product.

Smith & Nephew has retained non-exclusive rights to NeoCyte, a tissue-engineered cartilage currently in clinicals in the U.S. for ACL repair. In other orthobiologic initiatives, Smith & Nephew markets Jax, a calcium sulfate bone graft substitute material that may also have application as a carrier for pharmaceuticals used in treating bone infections, and also Viagraf DBM in five formulations: crunch, flex sheets, gel, paste and putty. The company's agreement with Osteotech also provides it with DBM products, as well.

Smith & Nephew is investigating the use of mesenchymal stem cells in the repair of bone, cartilage and ligaments. Products resulting from research are reportedly five to ten years from being available to patients if the company decides to invest substantially into development of the technology.

Stryker Biotech's OP-1 Implant, a human recombinant osteogenic protein, has been cleared for marketing in Australia and Canada for treatment of nonunion fractures of long bone; in Europe for nonunion fractures of the tibia; and in the U.S. under a Humanitarian Device Exemption for use as an alternative to autograft in certain recalcitrant long bone nonunions and in revision spine surgery. Stryker completed enrollment in a Japanese pivotal trial of OP-1 in non-cage, non-instrumented posterior lateral spine fusion and plans to combine OP-1 with its Ray TFC fusion cage. The company is also conducting a multicenter pivotal trial in the U.S. and Canada for posterolateral spine fusion using OP-1 Putty to treat degenerative spondylolisthesis, and anticipates that the evaluation of the 297 enrolled patients will be completed in late 2005.

Stryker also markets BoneSource, a calcium phosphate-based bone void filler cleared for CMF applications for years in the U.S. In 2003, Stryker received FDA clearance for BoneSource in orthopaedic applications (e.g. for bony voids not intrinsic to the stability of the bony structure) in extremities, spine, and pelvis.

Stryker is teamed with TEI Biosciences in an agreement that gives Stryker rights to the exclusive supply and distribution of TEI's TissueMend Soft Tissue Repair Matrix, which was cleared by FDA as a general surgical mesh for the repair and reinforcement of soft tissues where weakness exists. TissueMend has application for the repair of disorders of the joints and supporting tendinous, ligamentous and capsular supporting structures (excluding conditions related to spinal pathologies).

Synthes markets numerous structural and base allograft products through its distribution agreement with Musculoskeletal Transplant Foundation, along with XR calcium phosphate powder; ChronOs TCP wedges, blocks, cylinders and granules; and SRS and CRS, injectable carbonated apatite bone cements. SRS is cleared for broad orthopaedic applications outside the U.S., while its use in the U.S. is limited to

adjunctive or augmented treatment for unstable distal radius fractures and for bone void filling in extremities, spine and pelvis.

Teknimed markets a variety of HA and TCP synthetic bone graft substitutes including Ceraform 400 and Ceraform 200 (granules and blocks), Cementek LV (powder and injectable) and Tri HA+ in block form. All are cleared for use in the U.S. and Europe for orthopaedic applications.

Aside from TissueMend, TEI's orthobiologic platform consists of a remodelable collagen fiber scaffold enriched with a proprietary growth factor for use in spinal fusions and approaches for the rebuilding and repair of discs. The company's collaboration with Medtronic Sofamor Danek may lead to commercialization of spinal products. TEI has also generated ligament, tendon and cartilage prototypes and an injectable bone precursor cement with tissue specific signaling complexes.

Tepha's patented technologies center on the use of genetic engineering to create naturally-synthesized biopolymers (e.g. polyhydroxyalkanoate copolymer) that the company can process with a variety of mechanical properties. Tepha will develop resorbable polymers for use in such orthopaedic products as internal fixation devices, articular cartilage and meniscus regeneration devices, ligament and tendon grafts, spinal cages and bone graft substitutes.

The CryoSeal FS System from **ThermoGenesis** is used to prepare autologous hemostatic and adhesive surgical sealants from patient blood in approximately an hour. The company entered into an agreement with **Affinity Supplies** for distribution of the CryoSeal Fibrin Sealant System and Thrombin Processing Device (TPD) in Ireland, for use in orthopaedic and other specialties. ThermoGenesis expects product distribution in a majority of European countries before the end of 2005.

ThermoGenesis commenced shipments of its TPD to Biomet's Cell Factor Technologies subsidiary. The disposable kit, which produces stable, activated thrombin from a patient's blood in under 30 minutes, will enable Cell Factor to serve orthopaedic, spinal and maxillofacial applications in Europe, Canada and Asia.

Through expertise in signaling pathways that govern the recruitment, proliferation and differentiation of musculoskeletal cells, **TiGenix** develops cell-based tissue-engineered products for treatment of joint surface and bone defects. The company's first product is ChondroCelect, an autologous chondrocyte implant (ACI) that incorporates the company's proprietary genetic marker technology to improve the selection, characterization and expansion of cartilage-forming cell populations. TiGenix has been able to consistently grow hyaline cartilage *in vivo* and plans to leverage the technology to other orthopaedic applications. TiGenix is conducting a randomized, multi-national Phase III clinical trial comparing ChondroCelect to microfracture, the current standard of care, in the repair of symptomatic knee cartilage defects. Twelve hospitals will participate in the trial, in which 118 patients have already been enrolled. Results are expected in 2006. Further, the company filed an Investigational New Drug application for the product for the structural and functional repair of knee cartilage defects.

In the pipeline at TiGenix are ChondroCelect-P (which uses adult stem cell technology); technologies to treat osteochondral defects; and cell seeded bone matrices for the repair of large bone defects. Biomet's subsidiary, **IQL**, distributes the ChondroCelect ACI procedure in Spain and Portugal.

Tigenix signed a collaborative agreement with **ProStrakan** to research and develop new treatments for osteoarthritis and cartilage repair.

Tissue Genesis, in collaboration with the **University of Michigan**, seeks to develop 3D tensile connective tissues (e.g. tendons and ligaments) for replacement therapy. The company reportedly has already engineered self-organizing connective tissues without the use of artificial scaffolds, allowing cells within the tissue to generate their own extracellular matrix better suited to the eventual requirements of the tissue when implanted into the joint. Tissue Genesis uses a "Bio-Optimization System," an automated cell and tissue culture technology whose architecture reportedly provides a physiologic support system to ensure optimal conditions for cell growth and maintenance. Tissues would be "trained" in this system prior to their implantation.

Tissue Regeneration started operations to capitalize on the development of human tissue replacements for damaged or diseased soft tissue. The company's first product is a silk-based device and ACL tissue

engineering methodology, which entails seeding a silk-fiber mold with donor progenitor stem cells, incubating them and reimplanting them. Through a grant from the **National Institutes of Standards and Technology**, Tissue Regeneration will apply what it is learning about the ACL to the rotator cuff tendon in the shoulder and non-loading and loading bone grafts. The company expects to initiate ACL and rotator cuff trials in humans by the end of 2006.

Tredegar sold or assigned substantially all assets of its orthobiologics company to **Therics, LLC.** Therics has clearance in the U.S. to market a range of β-TCP bone graft products, all of which are manufactured using the company's novel TheriForm microfabrication process, which the company licensed from the Massachusetts Institute of Technology. Through the proprietary TheriForm technology, Therics is able to create precise three-dimensional (3D) geometries and architectures with controlled porosity and ingrowth channels. TheriForm machines can place synthetics, allograft or growth factors at specific geometric locations within the implant, and in gradients, to foster optimal bone ingrowth.

Products available from Therics include TheriFil, TheriRidge Block, TheriLok, TheriLink, TheriWedge and TheriMatrix, along with DBM and base allograft tissue.

Tutogen earned accreditation from the American Association of Tissue Banks. The company processes, develops, manufactures and markets allograft and bovine implants used in bone and soft tissue repair. Zimmer Spine distributes the company's line of structural and non-structural Puros Allografts for spinal indications. Tutogen also distributes Ligatech sports medicine allografts (bone-tendon-bone implants) through another network in the U.S. The company expects to shift its focus toward expanding its dental revenue and establishing business that is not as reliant on Zimmer, which owns a 30 percent stake in Tutogen. Further, in Italy, the company has partnered with new distributors and is seeking tissue bank approval status.

Researchers from the **University of British Columbia** and **Vancouver Coastal Health Research Institute** are developing a "living glue" which they hope might render revisions and other joint repairs obsolete within ten to 15 years. The glue combines growth factors, calcium, phosphate and stem cells from a patient's own bone marrow to promote bone regeneration and thus, better secure artificial joints. The

team will focus first on applications in revision hip surgery, and hopes to complete animal testing in four to five years. Future uses could include osteoporosis treatment and bone defect repair.

Vertebron's relationships with Musculoskeletal Transplant Foundation and **U.S. Tissue & Cell** provide the company with demineralized matrix devices and structural allografts in proprietary designs for spinal fusion applications, such as the PLF (posterolateral fusion) Allograft System.

Wright Medical Group markets a wide variety of bone graft substitute materials including OsteoSet, Allomatrix, MIIG (Minimally Invasive Injectable Graft), Ignite ICS (Injectable Cellular Scaffold), GraftJacket and CellPlex.

OsteoSet is a proprietary resorbable surgical grade calcium sulfate substitute used primarily in filling non-load bearing voids in long bones, spine, pelvis and extremities. Wright has developed an OsteoSet with DBM as well. The company's Allomatrix line (DBM+OsteoSet) includes an injectable putty, an injectable putty with cancellous bone granules (Allomatrix C); a custom bone graft putty; and Allomatrix DR Graft, optimized for application in smaller fractures due to its smaller particle size of cancellous bone granules. The MIIG family includes an injectable form of the company's calcium sulfate paste that hardens in the body, as well as a high-strength injectable calcium sulfate/calcium phosphate composite intended for use in treatment of distal radius, tibial plateau, pilon and certain spinal fractures. Wright's IGNITE ICS combines calcium sulfate, DBM and autologous bone marrow aspirate for the treatment of problem fractures and delayed nonunions, while CellPlex TCP Graft features a TCP cancellous scaffold for cell infiltration. CellPlex granules are packaged within the Infiltrate Marrow Infusion Chamber, which allows for minimally invasive aspiration and infusion of the patient's own bone marrow into the CellPlex matrix. To date, Wright is the only company to have received FDA clearance to market all of its allograft bone void fillers in the U.S.

Finally, Wright markets GraftJacket products through its relationship with LifeCell. The GraftJacket line includes Periosteum Replacement Scaffold for use as an onlay periosteal replacement scaffold for uncontained bone defects, a regenerative tissue matrix for hand surgery applications, tendon and ligament repair scaffolds and the Rotator Cuff Tendon Reinforcement Scaffold. The GraftJacket technology incorporates

biological substrate components (e.g. collagen, elastin, chondroitin sulfate, hyaluronic acid, fibroblast growth factor, etc.), which are processed to preserve the biochemical matrix and create an intact extracellular framework. The end result is a scaffold that allows for revascularization and cellular repopulation.

Xylos has developed a technology platform based on biosynthesized cellulose, a non-woven, multi-layered, 3D structure whose performance can be engineered for specific applications. Products being researched by Xylos include those for musculoskeletal repair. The company has developed and tested prototypes for rotator cuff repair.

Zimmer initiated the U.S. launch of the Zimmer Collagen Repair Patch, a chemically crosslinked, acellular sheet of collagen/elastin processed from porcine dermis and FDA-cleared for use in rotator cuff repair. The underlying technology originates from **Tissue Science Laboratories**, which markets the product as Permacol for non-ortho applications.

Zimmer acquired from **Revivicor** the worldwide exclusive distribution rights for genetically-engineered xenogeneic tissues for regenerative therapies. Zimmer will initially develop the technology for applications such as tendon, ligament, meniscus, cartilage, bone and spinal nucleus repair and replacement.

Zimmer is involved in distribution relationships with NeuColl and Tutogen. The company will also work with two universities to investigate gene therapy in the treatment of articular cartilage and meniscal damage.

Other companies with bone graft substitute materials on the market include **Asahi**, R and D Medical (Formagraft Collagen Bone Graft Matrix), **Taisho** and **Mitsubishi Pharma** (Biopex), **Toshiba Ceramics,** etc. Of note, many Japanese ceramics companies have diversified outside of semiconductors (their key strengths) into biologics, as evidenced by Toshiba Ceramics' approval to market its Neobone porous HA artificial bone filler.

Other companies with ACI technologies on the market outside the U.S. include **CellCoTec** (4CRT), **CellTec** (ChondroTec), **Interface** (Cartilink) and **Karocell** in Europe; **Cellontech** in Korea (Chondron), J-TEC in Japan, and **ProChon** (BioCart-II) in Israel.

Viscoelastics – Adhesion Prevention and OA Pain Relief

Among viscoelastics, hyaluronic acid (hyaluronan) plays the most prominent role in orthopaedics. A naturally occurring biopolymer, hyaluronic acid is found naturally in connective tissue, with its greatest concentrations in, among other places, the synovial fluid of articular joints. Its use, therefore, centers primarily on injection into the intra-articular space for relief of OA and restoration of joint fluid. Other viscoelastic products have found application in the prevention of post-surgical adhesions and failed back surgery syndrome.

Anika Therapeutics manufactures Orthovisc, an ultra-pure, medical grade, high molecular weight hyaluronic acid extracted from rooster and hen combs and used to treat pain caused by OA of the knee. Orthovisc treatment involves a series of three intra-articular injections one week apart. **DePuy Mitek** and sister company, **Ortho Biotech**, distribute Orthovisc in the U.S. and Mexico for treatment of knee OA pain, with Mitek targeting arthroscopists and orthopaedic surgeons and Ortho Biotech focusing on serving rheumatologists and other specialists. **Rivex** represents Anika in Canada, while a variety of distribution groups handle the product's sales and marketing in other areas outside the U.S. and Canada.

Anika also has developed the Incert family of chemically modified, cross-linked forms of hyaluronic acid for use in preventing surgical adhesions. The company initiated a human pilot clinical trial in the U.K. in early 2004 for Insert-S for the prevention of adhesions following spinal surgery. At the end of 2004, approximately two-thirds of the targeted 45 patients had been enrolled in the study and Anika had received CE Mark approval for the product. Pending results from the trial, Anika may initiate a pivotal PMA in the U.S.

Using bacterial fermentation, **Hyaltech** produces Fermathron, an injectable (five weekly injections) hyaluronan-based formulation for treatment of knee OA. Biomet distributes the CE Mark-approved product in most of Europe, with **Celltech** handling distribution in Germany.

Bioniche Life Science's Suplasyn, a sodium hyaluronate, is available in 30 countries outside the U.S. The company expects to launch SuplasynMD, a mini-dosage formula of Suplasyn for use in small joints, in most countries in Europe. In the U.S., Suplasyn is undergoing clinical trials, which could lead to regulatory submission with FDA.

Confluent's SprayGel Adhesion Barrier is a synthetic resorbable adhesion barrier based on *in situ* polymerized hydrogel polymers and delivery systems. The CE Mark-approved product is currently undergoing clinical trials for non-orthopaedic applications. However, Confluent is developing surgical sealing and adhesion barrier products for spine and orthopaedic surgery.

Fidia's Hyalgan was the first sodium hyaluronate therapy cleared by FDA (in 1997) for treatment of knee OA. **Sanofi-Synthelabo** markets the five-injection Hyalgan in the U.S., while an array of companies market Fidia's Hyalgan, Hyalubrix and Hyalart products in other geographic regions of the world.

In late September, FDA accepted the filing of a PMA Supplement that expands the indication of Hyalgan to include treatment of shoulder pain due to OA or OA in association with rotator cuff tears and/or adhesive capsulitis in patients who have failed to respond adequately to conservative therapies. Results from a U.S. clinical trial of 495 patients found injection site pain to be the only adverse event showing statistical significance vs. placebo.

FzioMed manufactures Oxiplex, a sterile, absorbable product that combines polyethylene oxide, sodium carboxymethylcellulose and calcium chloride. Oxiplex/SP Gel is a resorbable gel used outside the U.S. to reduce surgical adhesions following spine surgeries such as laminectomy, laminotomy and discectomy and to reduce pain and radiculopathy. **DePuy AcroMed** distributes Oxiplex/SP in Europe, while MSD obtained distribution rights for the product in various countries outside the U.S.

Oxiplex/SP is currently being investigated through a randomized, multicenter clinical trial in the U.S. for use in the reduction of pain and symptoms following lumbar disc surgery. The Oxiplex technology has also demonstrated its ability to act as a carrier for active substances used in the stimulation of bone

growth and cartilage repair, and the control of pain, infection or inflammation. In one study, Oxiplex alone demonstrated a positive stimulatory effect on bone healing. Additional acceleration of bone healing occurred with a combination of Oxiplex and a bone growth factor under development by Fziomed.

Oxiplex may also have potential to accelerate hemostasis, to promote healing and to treat OA.

Genzyme Biosurgery manufactures Synvisc, a biomaterial derived from hyaluronan used to treat the pain associated with knee OA. Administered through a series of three injections into the joint, Synvisc has been cleared for use in treating knee OA in the U.S., while its use in Europe and Canada includes both hip and knee applications. The product is available in more than 60 countries.

Genzyme filed for approval to market Synvisc in Japan for the treatment of OA pain and expects to receive approval for marketing there within two years. In late 2003, Genzyme began enrolling patients in a U.S. Phase III multicenter clinical trial for use of Synvisc in treatment of hip OA pain, while enrollment continues, as well, for Phase III trials in Europe for use of Synvisc in ankle and shoulder. Genzyme will continue to develop next-generation Synvisc products that would require fewer injections.

Integra LifeSciences' DuraGen Plus onlay collagen matrix received CE Mark certification as an adhesion barrier matrix for use after spine surgery. Integra launched the product in Europe in 2004. The company expects to increase its research and clinical activities in 2005, which may include a multicenter clinical trial that would support applying for FDA clearance on the DuraGen Plus Adhesion Barrier Matrix in the U.S.

Life Medical Sciences has developed a broad range of resorbable polymeric compositions whose characteristics can be tailor-made for specific therapeutic indications with particular application in prevention/reduction of post-surgical adhesions. The company's Relieve viscous gel products have been evaluated in a surrogate hand tendon model and in a feasibility study in spinal surgery. However, further development of these technologies will be deferred due to the company's limited resources and emphasis on other programs.

Cytori Therapeutics (formerly MacroPore Biosurgery) developed the SurgiWrap family of resorbable surgical thin films constructed from polylactide copolymers. MacroPore received clearance in Australia, Canada, Europe, Korea and Thailand for use of its films for the prevention of postsurgical adhesions in spinal applications. In 2004, the company sold off a significant portion of its Thin Film product line to MAST Biosurgery and entered into a distribution and supply agreement with Senko Medical Trading for rights to market Thin Film products in Japan. However, MacroPore received back a license of all rights to Thin Film technologies in the field of spine.

NeuColl's NeuVisc, a collagen-based intra-articular "implant," has shown promise as a single injection synovial fluid supplement to treat knee OA. Currently in clinical trials in the U.S., NeuVisc reportedly enhances the viscoelastic properties of synovial fluid more effectively than does hyaluronic acid.

In mid-2004, Angiotech Pharmaceuticals purchased the remainder of NeuColl's equity (it had owned 40 percent of the company). As a leader in drug-coated medical devices and biomaterials, Angiotech has developed sprayable adhesion prevention products, although none is available for use in orthopaedic or spine applications.

While **Novozymes** produces synthetic hyaluronic acid using microorganisms, the company plans to develop and produce hyaluronic acid for a variety of applications under a license agreement with **Hyalose**. Hyalose claims that its fermentation processes can produce hyaluronic acid less expensively than other technologies and the company seeks commercialization partners in the areas of wound healing, OA, device coatings, tissue engineering and anti-adhesion surgical devices. A collaboration with Novozymes could lead to production of hyaluronic acid through fermentation for use in arthritis and wound healing applications.

Q-Med's Durolane received CE Mark approval for single injection treatment of OA in both knee and hip. The non-animal stabilized hyaluronic acid features an insoluble gel of hyaluronic acid beads. Q-Med markets the product in the United Kingdom, France, Germany, Spain, Italy and the Nordic Countries and has filed for market approval in Canada. To date, more than 1.5 million Durolane treatments have taken place worldwide, with no emergence of any safety concerns.

Rottapharm has made GO ON hyaluronic acid available for the Spanish market as a complement in the integral treatment of OA.

Through its purchase of **Savient**'s global biologics manufacturing business (**Biotechnology General**), **Ferring Group** obtained worldwide rights to Euflexxa, a non-avian-derived biologic formulation of hyaluronic acid for use in treating knee pain due to OA. Savient and Ferring Pharmaceuticals will jointly market Euflexxa, which is expected to enter the marketplace in late 2005.

Seikagaku boasts development of Artz, the first hyaluronan joint fluid therapy commercially available for human use in treating OA. More than 119 million injections of the product have been sold worldwide since its introduction in 1987, with 2004 unit sales reaching 11 million. The once-weekly, five-injection therapy is available as Supartz through SNN in Europe and the U.S., while a number of other companies market the product in other parts of the world (**Kunming Baker Norton** in China and **MDM** in Italy) under the trade names Artz and Artzal. Artz products comprised the largest selling products for Seikagaku in fiscal 2004.

Through its core polysaccharide technology and with hyaluronan sourced from Lifecore Biomedical, **Stellar** has developed NeoVisc, a one percent solution of highly purified sodium hyaluronate used once weekly in a three-injection treatment of knee OA. The company distributes NeoVisc in Canada, where it has been available since 1997, while a variety of partners market the product in the Middle East, Latin America and parts of the Pacific Rim.

Stellar continues to move towards beginning its FDA clinical trials for NeoVisc in 2005 through a supply and license agreement with **Leitner Pharmaceuticals**. Clearance in Europe will be sought by Stellar's partner there, Pharmore.

TRB Chemedica specializes in the application of non-animal hyaluronan for medical purposes. The company's viscoelastic products include Ostenil sodium hyaluronate for treatment of OA pain primarily in the knee; Ostenil mini for OA in small joints (e.g. facets, saddle joint in thumb, interphalangeal joints of the fingers and toes, the proximal joint of the big toe, etc.); and Viscoseal, a solution of hyaluronan

used for pain relief, improvement in mobility and promotion of joint recovery following arthroscopic surgery or joint lavage. Chemedica also manufactures Hy-GAG and Hya-ject, distributed by Curasan and **Ormed**, respectively. Hy-GAG is typically administered over five sessions for treatment of arthrosis. Curasan's **Benelux** company also distributes Curavisc, a fermentation-derived viscoelastic for treatment of OA in all joints over a four-week course of treatment. **IDT** manufactures the product, which received CE Mark approval.

With its acquisition of all of the assets associated with **Gliatech**'s Adcon (resorbable carbohydrate) Gel technology, WMGI assumed distribution and sale of Adcon-L and Adcon-T/N anti-adhesion gel products. Both products are available outside the U.S. for treatment of post-surgical adhesions – Adcon-L following spinal surgery and Adcon-T/N following peripheral tendon and nerve repair. In mid-2005, based on discussions with FDA, Wright Medical withdrew its PMA submission for Adcon-L in the U.S. and will work towards a resubmission. Clearance for use of Adcon-T/N in the U.S. will require its own clinical study.

SUPPLIERS

In years past, activity in the supplier segment of the orthopaedic market has mirrored that for the overall market for orthopaedic products. The last 18 months have again borne out this dynamic, as exemplified by **Symmetry Medical**'s initial public offering in late 2004, the first for an orthopaedic-focused supplier.

Symmetry's key competitor, **Accellent**, expanded its orthopaedic platform with two acquisitions – **Campbell Engineering** and **Machining Technology Group** (MTG). Campbell brings Accellent additional expertise in precision machining and assembly of orthopaedic instrumentation and implants, while MTG specializes in rapid prototyping and manufacturing of specialized instruments for use in repair of the spine. MTG also manufactures implant-related instruments for hip, knee and trauma applications.

Additional consolidation came with the creation of **Orchid Orthopedic Solutions**, which brought together **BioCoat**, **Stealth Medical Technologies** and **Unique Instruments**. The new company focuses primarily on the hip and knee segments of the orthopaedic market, with capabilities in exotic alloys, coatings and instruments.

IonBond acquired **SwissCoating/PVT**, **ICC** and **Tinkap**; **Minnesota Rubber** and **QMR Plastics** purchased plastic injection molding manufacturer, **S&W Plast**ics; and **DRT Mfg**. (formerly **Dayton Reliable Tool & Mfg. Co.**) acquired **Mauch** from Ossür.

In response to a robust market, supplier companies expanded their facilities (e.g. **Doncasters** in Mexico, Precimed in Switzerland); increased their capabilities (e.g. **Allegheny** in titanium production, **Tornos** with new screw thread technology and **PAK Manufacturing**, **3D Machining**, **Specialized Medical Devices** and **Troy Innovative Instruments** in equipment) or gained capital infusion (e.g. **Paragon**, Precimed).

Finally, in looking toward the future of technology, Precimed formed a strategic partnership with **MBBS**. The companies will develop an autoclavable radio frequency identification system that is able to read and write through metal. The technology, which allows medical devices to be monitored, traced and tracked, may have application in computer aided and minimally invasive surgery, surgical technique reference guides, etc.

SUMMARY

Over the next decade, the worldwide orthopaedic industry should experience steady growth due to

- An aging population
- A more active and longer-lived population
- An increasingly obese population
- Increased involvement of the world's people in their own healthcare (and that of their children and parents)
- Increased marketing to consumers on the part of orthopaedic companies, surgeons and hospitals
- Further penetration of orthopaedic procedures in less developed nations
- Technologies that expand application of orthopaedic procedures to younger age groups

THE COMPETITIVE ORTHOPAEDIC ENVIRONMENT

In 2004, 77 percent of global orthopaedic revenues came from the efforts of the ten largest orthopaedic companies in the world. Exhibit 2 lists these companies and their estimated sales by key product areas.

EXHIBIT 2
THE 2004 WORLDWIDE ORTHOPAEDIC MARKET:
SALES FOR THE TOP TEN COMPANIES AND ALL OTHERS BY MARKET SEGMENT
($MILLIONS)

Company	*Recon*	*FF*	*AR/ST*	*Spine*	*Other**	*Total*
Aesculap	$157	$31	$13	$85	$95	$382
Biomet	$854	$83	$42	$97	$486	$1,562
ConMed	$0	$0	$205	$0	$129	$334
JNJ	$1,905	$105	$249	$702	$466	$3,427
MSD	$0	$0	$0	$1,300	$513	$1,813
SNN	$750	$298	$441	$0	$130	$1,619
Stryker	$1,651	$417	$250	$249	$918	$3,485
Synthes	$0	$1,038	$0	$462	$296	$1,796
WMGI	$222	$7	$0	$0	$68	$297
Zimmer	$2,340	$173	$13	$134	$195	$2,856
Total Top Ten	**$7,880**	**$2,151**	**$1,214**	**$3,029**	**$3,295**	**$17,569**
Total Others	**$773**	**$500**	**$705**	**$621**	**$2,765**	**$5,365**
Total Market	***$8,653***	***$2,651***	***$1,919***	***$3,650***	***$6,060***	***$22,934***

Notes:

*Other includes orthobiologics, power equipment, casting materials, soft goods, bracing systems, bone growth stimulators, craniomaxillofacial fixation products, navigation (specific to orthopaedics), cement and cement mixing/delivery systems, infection control equipment, pulsed lavage/irrigation systems, etc.

Biomet and Zimmer exclude sales for dental products.
ConMed includes only arthroscopy and power instrument sales.
MSD excludes neurosurgery product sales.
SNN's sales include those for orthopaedics and arthroscopy (a portion of the company's endoscopy division), but exclude wound management product revenues.
Stryker excludes sales for patient handling equipment, physiotherapy products and endoscopic equipment used in non-orthopaedic areas.

More than 200 companies market orthopaedic products worldwide, the vast majority with sales under $5 million. Those with 2004 sales in excess of $5 million are profiled in Exhibit 3, which summarizes esti-

mated sales for these companies along with the breadth and depth of their product offerings. Please note that only orthopaedic product revenues are captured in the Exhibit.

EXHIBIT 3
ORTHOPAEDIC COMPANIES WITH 2004 SALES >$5MM:
ESTIMATED SALES AND BREADTH/DEPTH OF PRODUCT LINE

Company	*2004 Sales*	*Recon*	*FF*	*AR/ST*	*Spine*	*Biologics*	*BGS*	*Other*
aap	$15MM	✓	✓			✓		✓
Abbott Spine	$60-$70MM				✓	✓		
Acumed	$50-$60MM		✓					
Aesculap	$375-$400MM	✓	✓	✓	✓	✓		✓
Alphatec	$20-$30		✓		✓	✓		
Anika	$11MM					✓		
Anspach	$80-$90MM							✓
Arthrex	$200-$225MM	✓	✓	✓		✓		
ArthroCare	$133MM			✓	✓			✓
Ascension	$5-$10MM	✓				✓		
Baumer	$10-$20MM	✓	✓		✓	✓		
Biocomposites	$5-$10MM			✓		✓		
Biomet	$1.6 billion	✓	✓	✓	✓	✓	✓	✓
Blackstone	$45-$55MM				✓	✓		
ConMed	$334MM		✓	✓				✓
Corin	$46MM	✓	✓	✓	✓	✓		✓
dj Ortho	$256MM						✓	✓
Encore	$69MM	✓	✓		✓			✓
Eska	$10-$20MM	✓						
Exactech	$82MM	✓				✓		
Fidia	$100-$125MM					✓		✓
Future Medical	$20-$25MM			✓				

(Continued on the following page)

EXHIBIT 3
ORTHOPAEDIC COMPANIES WITH 2004 SALES >$5MM:
ESTIMATED SALES AND BREADTH/DEPTH OF PRODUCT LINE
(continued)

Company	*2004 Sales*	*Recon*	*FF*	*AR/ST*	*Spine*	*Biologics*	*BGS*	*Other*
Fournitures Hospitalieres	$40-50MM	✓	✓		✓	✓		
Genzyme	$225-$250MM					✓		
Globus	$10-$20MM				✓	✓		
Hand Innovations	$30-$40MM		✓					
Innovation Sports	$25-$35MM							✓
Integra	$15-$20MM		✓		✓			✓
IsoTis	$25MM					✓		
Japan MDM/Ortho Development	$110-$120MM	✓			✓	✓		
Japan Medical Materials	$80-$90MM	✓			✓	✓		
JNJ	$3.42 billion	✓	✓	✓	✓	✓		✓
JRI	$20-$30MM	✓						
Kanghui	$5-$10MM	✓						
Karl Storz	$75-$100MM			✓				
KMI	$10-$15MM		✓					✓
Kyphon	$213MM				✓	✓		
Lima	$10-$20MM	✓	✓					✓
Mathys	$40-$50MM	✓				✓		
Medacta	$20-$25MM	✓						
Medtronic	$1.8 billion				✓	✓		✓
MicroAire	$40-$50MM							✓
MTF	$225-$250MM					✓		
Nexa	$5-$10MM	✓	✓	✓				✓
NuVasive	$38MM				✓	✓		

(Continued on the following page)

EXHIBIT 3
ORTHOPAEDIC COMPANIES WITH 2004 SALES >$5MM:
ESTIMATED SALES AND BREADTH/DEPTH OF PRODUCT LINE
(continued)

Company	*2004 Sales*	*Recon*	*FF*	*AR/ST*	*Spine*	*Biologics*	*BGS*	*Other*
Orthofix	$257MM		✓	✓			✓	✓
ORTHOsoft	$5-$10MM					✓		✓
Orthovita	$25MM					✓		
Ossür/Royce	$75-$100MM							✓
Osteomed	$40-$50MM		✓			✓		✓
Osteotech	$89MM					✓		
Richard Wolf	$60-$70MM			✓	✓			
RTI	$83MM					✓		
SanOrtho	$10-$15MM	✓	✓			✓		
Scient'x	$15-$25MM				✓	✓		
SeaSpine	$5-$10MM				✓			
Seikagaku	$140-$150MM					✓		
Serf	$10-$15MM	✓						
Showa Ika	$35-$45MM	✓	✓		✓			
Signus	$10-$15MM				✓			
SBI	$15-$20MM	✓	✓	✓	✓	✓		✓
SNN	$1.6 billion	✓	✓	✓	✓	✓	✓	✓
Sodem	$5-$10MM							✓
StelKast	$5-$10MM	✓						
Stryker	$3.48 billion	✓	✓	✓	✓	✓		✓
Surgical Dynamics	$5-$10MM			✓				
Surgicraft	$10-$15MM			✓	✓			
Surgival	$10-$20MM	✓	✓		✓			
Synthes	$1.8 billion		✓		✓	✓		✓

(Continued on the following page)

EXHIBIT 3
ORTHOPAEDIC COMPANIES WITH 2004 SALES >$5MM:
ESTIMATED SALES AND BREADTH/DEPTH OF PRODUCT LINE
(continued)

Company	*2004 Sales*	*Recon*	*FF*	*AR/ST*	*Spine*	*Biologics*	*BGS*	*Other*
Synvasive	$5-$10MM							✓
Tornier	$60-$70MM	✓	✓					
Townsend	$15-20MM							✓
Tutogen	$10-$15MM					✓		
United Orthopedic	$10-$20MM	✓						
Waldemar Link	$150-$200MM	✓	✓	✓	✓			✓
Wright Medical	$297MM	✓	✓			✓		
Zimmer	$2.9 billion	✓	✓	✓	✓	✓		✓

Orthopaedics (from joint replacement to bone growth factors) remains one of the healthiest segments of the worldwide medical device industry. Companies continue to consolidate through strategic alliances that provide product, geographic and manufacturing efficiencies. An influx of new companies will also continue, as numerous opportunities exist for innovation in both traditional musculoskeletal repair and the use of biologic materials to treat musculoskeletal ailments.

Source: Knowledge Enterprises, Inc., 147 Bell Street, Suite 303, Chagrin Falls, Ohio, 44022. 440 247 9051 (phone); 440 247 9053 (fax); e-mail: knowledge@orthoworld.com; Web Address: www.theorthopeople.com

APPENDICES

EXHIBIT APP-1
RECONSTRUCTIVE DEVICE COMPANIES

Company	*Hip*	*Knee*	*Shoulder*	*Hand/ Wrist*	*Elbow/ Radial Head*	*Digits*	*Ankle*
aap	✓	✓	✓				
Aesculap	✓	✓					
Aptis				✓			
ARGE	✓	✓					
Argomedical	✓		✓				
Arthrex			✓				
Ascension				✓	✓		
Australian Surgical Design & Manufacture		✓					
Baumer	✓	✓	✓		✓		✓
Benex	✓						
Beznoska	✓	✓	✓				
Biomet	✓	✓	✓	✓	✓		
BioPRO	✓	✓	✓	✓	✓	✓	
Bioprofile				✓	✓		
Biotechni	✓		✓				
Biotek			✓		✓		
Ceraver	✓	✓	✓				
Citieffe	✓	✓					
ConforMIS		✓					
Corin	✓	✓	✓				✓
Cousin Biotech	✓	✓					
Dedienne Sante	✓	✓					
DePuy	✓	✓	✓	✓	✓	✓	✓
Disc-O-Tech	✓						
Encore	✓	✓	✓				
Endotec	✓	✓	✓				✓
Eska	✓	✓		✓		✓	✓
Euros	✓	✓					✓
Exactech	✓	✓	✓				
FH Orthopedics	✓	✓					✓
FII	✓	✓					
Finsbury	✓	✓		✓			
Fixano	✓	✓	✓				
Global Orthopaedic Technology	✓	✓					
Groupe Lepine	✓	✓	✓				
Hardik	✓						
Hayes Medical	✓	✓					
Implantes Fico	✓	✓					

(Continued on the following page)

EXHIBIT APP-1
RECONSTRUCTIVE DEVICE COMPANIES
(continued)

Company	*Hip*	*Knee*	*Shoulder*	*Hand/ Wrist*	*Elbow/ Radial Head*	*Digits*	*Ankle*
Implants Industrie	✓	✓	✓				
Implants International	✓	✓		✓			
Impliant	✓						
Inor Orthopaedics	✓	✓			✓		
Integra							✓
Japan MDM/Ortho Development	✓	✓					
Japan Medical Materials	✓	✓	✓		✓		✓
JRI	✓	✓					
Kinamed	✓	✓					
KMI				✓	✓		
Lafitt	✓	✓					
Lima	✓	✓	✓				
Mathys	✓	✓	✓			✓	
Medacta	✓	✓					
Medicalex-Francemed					✓		
Merete	✓						
Mizuho	✓						
Narang	✓						
Nexa						✓	
NexMed	✓	✓					
OMNI Life Science	✓						
Orthofix						✓	
Orthopaedic Innovation	✓						
Orthosurgical				✓			
Ortosintese	✓	✓	✓				
OsteoMed						✓	
Peter Brehm	✓	✓					
PLUS	✓	✓	✓			✓	
Portland	✓						
Protetim	✓	✓	✓	✓	✓		✓
Roth Medical	✓						
SanOrtho	✓	✓					
SBI				✓	✓		
Seremm	✓						
SERF	✓	✓					
Sgarlato						✓	
Showa Ika	✓						

(Continued on the following page)

EXHIBIT APP-1
RECONSTRUCTIVE DEVICE COMPANIES
(continued)

Company	*Hip*	*Knee*	*Shoulder*	*Hand/ Wrist*	*Elbow/ Radial Head*	*Digits*	*Ankle*
Small Bone Innovations				✓	✓	✓	
Smit Medimed	✓						
Smith & Nephew	✓	✓	✓		✓		
Stanmore	✓	✓	✓				
StelKast	✓	✓					
Stryker	✓	✓	✓	✓	✓		
Stuckenbrock				✓			
Sushrut	✓						
Symbios	✓						
Tantum	✓						
Tecres				✓			
Tianjin	✓						
Tornier	✓	✓	✓		✓		✓
Treu	✓						
Uma Surgicals	✓		✓				
United Orthopedic	✓	✓					
Van Straten	✓	✓	✓				✓
Waldemar Link	✓	✓		✓	✓		✓
Whiteside	✓	✓					
Wright	✓	✓	✓	✓	✓	✓	
Zimmer	✓	✓	✓		✓	✓	

EXHIBIT APP-2
FRACTURE REPAIR COMPANIES

Company	*ExFix*	*IM Nail*	*Hip Fix*	*Plates/ Screws*	*Bone Growth - Trauma*
aap		✓		✓	
Acumed	✓	✓		✓	
Aesculap		✓	✓		
Agee	✓				
ALBU Medical Implanta		✓	✓	✓	
AOS		✓			
Argomedical		✓		✓	
Arthrex				✓	
Austofix		✓	✓		
Australian Surgical Design & Manufacture				✓	
Baumer	✓	✓		✓	
Benex	✓			✓	
Beznoska	✓			✓	
Bidoia		✓		✓	
Biomet	✓	✓	✓	✓	✓
BioPRO		✓		✓	
Bio-Prot			✓		
Biotek		✓			
Citieffe	✓	✓		✓	
Corin		✓	✓		
Creative Medical Designs				✓	
Dedienne Sante				✓	
DePuy	✓	✓	✓	✓	
Disc-O-Tech		✓			
dj Orthopedics					✓
DVO		✓		✓	
Enztec				✓	
Erothitan Titanium Implante				✓	
FH Orthopedics		✓			
Forward Medical					✓
GMReis	✓	✓		✓	
Groupe Lepine				✓	
Hand Innovations				✓	
Hardik	✓	✓	✓	✓	
Icotec				✓	
Implantes Fico				✓	
Implants Industrie				✓	
Implants International		✓			

(Continued on the following page)

EXHIBIT APP-2
FRACTURE REPAIR COMPANIES
(continued)

Company	*ExFix*	*IM Nail*	*Hip Fix*	*Plates/ Screws*	*Bone Growth - Trauma*
Inor Orthopaedics	✓	✓	✓	✓	
Integra				✓	
ITS		✓			
Japan MDM/Ortho Development	✓	✓	✓	✓	
Japan Medical Materials			✓		
Kanghui		✓	✓	✓	
KMI				✓	
Lafitt		✓			
Lima	✓	✓			
Martin				✓	
Medartis				✓	
Medicalex-Francemed		✓		✓	
Medicor		✓		✓	
Merete			✓	✓	
Millennium Medical				✓	
Mizuho			✓		
Narang	✓			✓	
Orthofix	✓	✓	✓	✓	✓
Orthopedic Designs		✓	✓		
Orthosurgical				✓	
Ortosintese	✓	✓			
OsteoMed				✓	
PLUS		✓			
Protetech	✓				
Protetim		✓			
Roth Medical	✓	✓	✓	✓	
SanOrtho		✓		✓	
Scruples Medical	✓			✓	
Showa Ika			✓		
Small Bone Innovations	✓		✓	✓	
Smit Medimed	✓		✓	✓	
Smith & Nephew	✓	✓	✓	✓	
Solco Biomedical	✓	✓	✓	✓	
Stryker	✓	✓	✓	✓	
Surgival		✓		✓	
Sushrut	✓		✓	✓	
Synthes	✓	✓	✓	✓	

(Continued on the following page)

EXHIBIT APP-2
FRACTURE REPAIR COMPANIES
(continued)

Company	*ExFix*	*IM Nail*	*Hip Fix*	*Plates/ Screws*	*Bone Growth - Trauma*
Tantum		✓	✓	✓	
Teknimed		✓			
Tianjin				✓	
Treu	✓	✓			
TriMed				✓	
Triage				✓	
U&I	✓	✓		✓	
Uma Surgicals	✓	✓		✓	
Waldemar Link				✓	
Wright				✓	
Zimmer	✓	✓	✓	✓	

EXHIBIT APP-3
ARTHROSCOPY/SOFT TISSUE/SPORTSMED COMPANIES

Company	*Arthroscopy Equipment*	*Soft Tissue Fixation*	*Artificial Ligament/ Tendon*	*Biological Repair/ Replacement*
Aesculap	✓	✓		✓
Angiotech				✓
ARS Arthro				✓
Arthrex	✓	✓		✓
ArthroCare	✓	✓		
Artimplant		✓		
Axya		✓		
Biocomposites		✓		
Biomet	✓	✓		✓
Bio-Prot		✓		
Biosyntech				✓
BioTissue Technologies				✓
Bonutti		✓		
CellGenix				✓
CellTec				✓
Citieffe		✓		
co.don				✓
ConMed	✓	✓		
Corin		✓	✓	
Cousin Biotech		✓	✓	
CrossCart				✓
CryoLife				✓
DePuy	✓	✓		✓
Ellis Development		✓	✓	
FH Orthopedics		✓	✓	
Fidia				✓
Fixano		✓	✓	
Future Medical	✓	✓		
Genzyme				✓
Inion		✓		
J-TEC				✓
Karl Storz	✓	✓		
KFx Medical		✓		
MedicineLodge		✓		
Millenium				✓
MTF				✓
Olympus	✓			
Ortheon		✓		

(Continued on the following page)

EXHIBIT APP-3
ARTHROSCOPY/SOFT TISSUE/SPORTSMED COMPANIES
(continued)

Company	*Arthroscopy Equipment*	*Soft Tissue Fixation*	*Artificial Ligament/ Tendon*	*Biological Repair/ Replacement*
Orthofix		✓		
Orthogen				✓
Orthomed		✓	✓	
ReGen				✓
Richard Wolf	✓	✓		
RTI				✓
Scandius		✓		
Science for Bio Materials		✓		
Small Bone Innovations		✓		
Smith & Nephew	✓	✓		✓
Stryker	✓	✓		✓
Surgicraft		✓	✓	
Teknimed		✓	✓	
TiGenix				✓
Wright		✓		✓
Xiros		✓	✓	
Zimmer		✓		✓

EXHIBIT APP-4
SPINAL IMPLANTS/INSTRUMENTATION COMPANIES

Company	*Fusion*	*Motion Preservation/ Dynamic Stabilization*	*Disc Augmentation*	*Facet Repair/ Replacement*	*Bone Growth - Spine*	*Osteoplasty/ Cement*
Abbott Spine	✓	✓				
ABS						✓
Advanced Medical Technologies	✓					
Aesculap	✓					
Allez Spine	✓					
Alphatec	✓	✍				
Altiva	✓					
Amedica		✍				
Anatomica Spine	✓					
Anulex			✍			
Applied Spine Technologies		✍				
Archus				✓		
ArthroCare						✓
Aspine	✓					
Atlas Spine	✓					
AxioMed		✍				
Biomet	✓	✍	✍		✓	✓
Bio-Prot	✓					
Biotechni	✓					
Biotek	✓					
Blackstone	✓	✍				
BoneSupport						✓
Cardinal						✓
Cervitech		✓				
Co-Ligne	✓					
Corin	✓		✍			
Cousin Biotech		✓				
Custom Spine	✓	✍				
DePuy	✓	✓	✍			✓
Disc Dynamics			✓			
Disc-O-Tech						✓
dj Orthopedics					✓	
Dynamic Spine			✍			

✍ In development

✓ Commercialized or in human clinical studies

(Continued on the following page)

EXHIBIT APP-4
SPINAL IMPLANTS/INSTRUMENTATION COMPANIES
(continued)

Company	*Fusion*	*Motion Preservation/ Dynamic Stabilization*	*Disc Augmentation*	*Facet Repair/ Replacement*	*Bone Growth - Spine*	*Osteoplasty/ Cement*
Encore	✓					
Endius	✓					
Facet Solutions				✓		
FH Orthopedics	✓					
Flexuspine		✍				
Gentis			✍			
Globus	✓	✓				
GMReis	✓	✓				
Hardik	✓					
Highgate Orthopedics	✓	✍				
Impliant		✍		✓		
Innovasis	✓					
Inor Orthopaedics	✓					
Integra						✓
Intrinsic Therapeutics			✍	✓		
Japan MDM/Ortho Development	✓					
Japan Medical Materials	✓					
K2M	✓	✍	✍			
Kyphon						✓
Lanx	✓					
LDR	✓	✓				
LifeSpine	✓	✍				
Medicalex-Francemed	✓					
Medicrea	✓					
Medtronic	✓	✍				✓
Merete	✓					
N Spine	✓	✍				
Narang	✓					
Nexgen Spine		✍				
NuVasive	✓	✓	✍			

✍ In development

✓ Commercialized or in human clinical studies

(Continued on the following page)

EXHIBIT APP-4
SPINAL IMPLANTS/INSTRUMENTATION COMPANIES
(continued)

Company	*Fusion*	*Motion Preservation/ Dynamic Stabilization*	*Disc Augmentation*	*Facet Repair/ Replacement*	*Bone Growth - Spine*	*Osteoplasty/ Cement*
Olsen Medical	✓					
Ortho Sol	✓	✍				
Orthofix					✓	
Orthonics			✍			
Orthopedic Alliance	✓					
Orthopedic Sciences	✓					
Orthopeutics			✍			
Ortosintese	✓					
Paradigm Spine		✍				
Peter Brehm	✓					
Pioneer	✓	✓				
Pisharodi Surgicals	✓	✍				
Quantum				✓		
Ranier		✍				
Raymedica			✓			
Replication Medical			✓			
Scient'x	✓	✓				
SeaSpine	✓	✍				
Showa Ika	✓					✓
Signus	✓	✍	✍			
Smit Medimed	✓					
Solco Biomedical	✓					
SpinalMotion		✓				
Spine Motion		✍				
Spine Wave			✓			✓
SpineMedica		✍				
SpineVision	✓					
St. Francis		✓				
Stryker	✓	✓	✍			✓
Surgival	✓					

✍ In development

✓ Commercialized or in human clinical studies

(Continued on the following page)

EXHIBIT APP-4
SPINAL IMPLANTS/INSTRUMENTATION COMPANIES
(continued)

Company	*Fusion*	*Motion Preservation/ Dynamic Stabilization*	*Disc Augmentation*	*Facet Repair/ Replacement*	*Bone Growth - Spine*	*Osteoplasty/ Cement*
Sushrut	✓					
Synthes	✓	✍	✍			✓
Tecres						✓
Teknimed						✓
Theken	✓	✍				
TranS1	✓					
Treu	✓					
U&I	✓					
U.S. Spine	✓	✍	✍	✓		
Ulrich	✓	✍				
Uma Surgicals	✓					
Vertebron	✓	✍				
X-Spine	✓	✍				
Zimmer	✓	✓	✓			

✍ In development

✓ Commercialized or in human clinical studies

EXHIBIT APP-5
BIOLOGICS & CEMENT COMPANIES

*Company**	*Synthetics*	*Allograft/ DBM*	*Osteoinductives*	*Bone Cement*
aap	✓			✓
Aastrom			✓	
Abbott Spine	✓			
ABS				✓
Acologix			✓	
Aesculap		✓		
AlloSource		✓		
Alphatec Spine		✓		
Altiva	✓			
Angiotech	✓		✍	
Apatech	✓			
ArthroCare				✓
Ascension	✓			
Baumer	✓		✓	
Berkeley	✓			
Bidoia				✓
Biocomposites	✓			
Biomet	✓	✓	✍	✓
Biosyntech	✓			
Blackstone	✓			
Bone Support	✓			
CAM Implants	✓			
Ceramisys	✓			
Ceraver	✓			✓
Collagen Matrix	✓			
Corin	✓			✓
Cryolife		✓		
Curasan	✓			
DePuy	✓	✓	✍	✓
Doxa	✓			
DRG	✓			
Exactech		✓		✓
Etex	✓			

* Only those companies that have at least one product on the market somewhere in the world.

✍ In development

✓ Commercialized or in human clinical studies

(Continued on the following page)

EXHIBIT APP-5
BIOLOGICS & CEMENT COMPANIES
(continued)

*Company**	*Synthetics*	*Allograft/ DBM*	*Osteoinductives*	*Bone Cement*
FH Orthopedics	✓			✓
Global Orthopaedic Technology	✓			
GMReis	✓		✓	
Integra			✍	✓
IsoTis	✓	✓		
Japan MDM/Ortho Development	✓	✓		
Japan Medical Materials	✓			
Kasios	✓			
Kuros	✓			
Kyphon	✓			✓
LDR	✓			
LifeCell		✓		
Lima				✓
Mathys	✓			
MDT	✓	✓	✓	
Medartis	✓			
Medicrea	✓			
Millenium Biologix	✓		✓	
MTF		✓	✍	
Nexa	✓			
NovaBone	✓			
NuVasive		✓		
OBI	✓			
Olympus	✓			
Orthocon	✓			
OrthoLogic			✓	
Orthomed	✓			
Orthovita	✓			
Ossacur	✓			
Osteotech		✓		

* Only those companies that have at least one product on the market somewhere in the world.

✍ In development

✓ Commercialized or in human clinical studies

(Continued on the following page)

EXHIBIT APP-5
BIOLOGICS & CEMENT COMPANIES
(continued)

*Company**	*Synthetics*	*Allograft/ DBM*	*Osteoinductives*	*Bone Cement*
Pegasus	✓			
RTI		✓		
SanOrtho	✓			
Science for Bio Materials	✓			
Scient'x	✓			
Skeletal Kinetics	✓			
Smith & Nephew	✓	✓		✓
Stryker	✓	✓	✓	✓
Synthes	✓	✓		
Tecres				✓
Teknimed	✓			
Theken Spine	✓	✓		
Tutogen		✓		
Vertebron	✓	✓		
Wright	✓	✓		✓
Zimmer	✓	✓	✍	✓

* Only those companies that have at least one product on the market somewhere in the world.

✍ In development

✓ Commercialized or in human clinical studies