Beyond INFUSE: Spine Community Searches For Answers, Alternatives

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Executive Summary

Medtronic's INFUSE bone morphogenetic protein is the only product in the musculoskeletal industry that has changed the bar in terms of bone healing, and it is under fire for complications related to off-label use. As regulators and payors crack down on INFUSE and hospitals restrict access to the product, surgeons are seeking alternatives and there are a number of companies lining up to fill the void.

The medical technology arena is home to a number of "game-changing" technologies that initially took the industry by storm only to see their meteoric rise followed by a precipitous fall. The drug-eluting stent market is one example marked by an evolutionary (indeed some would say revolutionary) technology that was widely and broadly adopted for the first few years following market introduction, but took a hit when concerns surfaced about off-label use and potential complications. Even though those concerns were largely ameliorated, the market never did return to its initial fervor. More recently, studies suggesting implantable cardioverter defibrillators (ICDs) are often used outside of recommended guidelines and have thrown the cardiac rhythm management arena into a quandary as well. (See "Cardiac Rhythm Management Market Faces Continued Challenges Ahead" - Medtech Insight, August 2011.) And now, a similar but potentially even more serious story is playing out in the musculoskeletal industry.

Only one product in the musculoskeletal arena has changed the bar in terms of bone healing and that is INFUSE, Medtronic Inc.'s blockbuster bone morphogenetic protein (BMP), which accounts for 40% of the $1.74 billion market for bone replacement materials. Now, however, INFUSE is being slammed by a backlash from professional societies, and the inevitable emergence of class action lawsuits. Safety issues originating from the use of INFUSE in the cervical spine mushroomed into allegations of off-label promotion, triggering a Department of Justice (DOJ) investigation in 2008 that was expanded in April 2011. Moreover, conflict of interest issues heightened in June when the Senate Finance Committee initiated an investigation of
Medtronic physician consultants for not disclosing or reporting serious complications or adverse events associated with INFUSE. To top it all off, the entire June 28, 2011, issue of *The Spine Journal* was devoted to INFUSE with a focus on many of these issues.

**Off-Label Crack Down**

In July, Medtronic announced that it will make all INFUSE patient data, both published and unpublished, and Food and Drug Administration (FDA)-filed adverse event reports available to *Yale University* for an independent and comprehensive review of the entire body of evidence on the BMP product. With a $2.5M grant, Yale will conduct two fully independent, third-party systematic reviews of the safety and effectiveness of INFUSE. Medtronic is hoping that the Yale review, the results of which should be available in mid 2012, will quickly put safety and trust issues to rest before mounting legal issues take hold. In the meantime, regulators and payors are cracking down on off-label use and some hospitals are restricting access to INFUSE, requiring surgeons to seek an alternative as a cost-saving measure.

With off-label use as high as 85% (INFUSE is FDA approved only for use in anterior lumbar interbody spinal fusion [ALIF], tibial fractures, and dental procedures), Medtronic recently initiated a 534-patient, Investigational Device Exemption (IDE) study evaluating the safety and efficacy of INFUSE in conjunction with the *CAPSTONE* and *CD* Spinal Implant Systems for one- to two-level fusion using a transformaminal lumbar (TLIF) approach in patients with lumbrosacral degenerative disease. These data will be used to expand approval of INFUSE in spinal fusion beyond the narrow indication of single-level ALIF. However, this is not Medtronic’s first attempt to gain approval for its BMP for broader spinal indications, and this time the bar is set much higher. Last year, the company tried unsuccessfully to obtain approval for its BMP for posterolateral fusion. However, the issue of cancer risk reared its ugly head, and as a result, Medtronic received a nonapproval letter in December.

**DBMs Versus INFUSE**

Medtronic’s $123 million acquisition of Osteotech Inc. last year was a strategic attempt to offset the anticipated decline in its biologic product revenues, which reached $884 million (or 20% of the company’s spine division) in FY 2011, ending in May. [See Deal] Of this, BioMedGPS estimates that INFUSE sales accounted for approximately $740 million, with over 92% from sales in the US, trending downward for the last two years. Now, with two of the leading demineralized bone matrix (DBM) products in their bags—Osteotech’s *Grafton* and MagniFuse—Medtronic reps are incentivized to sell DBM products over INFUSE, as they are lower-cost and higher-margin products.

**Outlook Uncertain**

To the surprise of many, Medtronic’s Q1 2012 biologic revenues posted positive gains of +2% driven by Osteotech’s $23 million contribution to revenues. For the quarter, INFUSE sales declined by 8%, an improvement from the upper-teens decline seen after *The Spine Journal* articles were published. Whether this represents a rebound or results from overstocking of accounts with INFUSE remains to be seen. Some analysts are predicting double-digit declines this year, while other naysayers are projecting that INFUSE revenues will drop by half in the next two years as class action lawsuits come into play. Furthermore, a likely (substantial) fine from the DOJ makes a possible divestiture...
of the product not out of the question.

Even though there are nearly 200 bone replacement products on the US market, according to BioMedGPS’ SmartTRAK Bone Replacement module, there is no other product that comes close to INFUSE in being able to consistently and reliably regenerate bone. As a result, the growth factor segment continues to dominate this market in the US, with estimated sales of over $703 million in 2010. (See Exhibit 1.) The only other BMP on the US market was Stryker Corp.’s OP-1, purchased in February by Olympus Corp. for $60 million. [See Deal] Olympus is distancing itself from INFUSE by renaming the product Opgenra and calling it an eptoterin alfa instead of a BMP. Opgenra is in the process of being launched in the UK and Germany for posterior lateral fusions and will be launched in other European Union countries later this year.

EXHIBIT 1
US Market For Bone Replacement Products By Segment, 2010

| Machined Bone and Allograft | $420,000,000 |
| DBM | $283,000,000 |
| Growth Factors | $703,120,000 |
| Synthetic | $246,000,000 |
| Stem Cell | $90,680,000 |
| **TOTAL Bone Replacement** | **$1,742,800,000** |

Other Growth Factor Products

But there are other products on the horizon. For example, BioMimetic Therapeutics Inc. is awaiting word from the FDA outlining post-panel requirements and timeline for approval of its Augment Bone Graft, a beta-tricalcium phosphate with recombinant human platelet-derived growth factor (rhPDGF-BB) for foot and ankle fusions. The product received a positive panel recommendation in May. In June, the company announced that it was delaying planned IDE pilot trials for Augment for interbody lumbar spine fusion until it receives clarity from the FDA on the foot and ankle Premarket Application, which should come in September. In the meantime, BioMimetic has submitted a CE mark application and expects to gain European market approval for Augment BG for foot and ankle fusion and distal radius fusion in 2012 based on completion of a 125-patient, 10-center, open-label foot and ankle trial with a primary end point of percent fusion at nine months. The company also applied
for approval in Australia for foot and ankle fusion and expects to be approved in that country in 2012.

Also targeting the foot and ankle market is privately held BioSET Inc. with its proprietary B2A, a synthetic peptide that mimics the effect of BMP-2 on bone growth and healing. In February, the company announced the start of a Canadian trial comparing B2A to iliac crest bone graft for foot and ankle fusion. This BMP-2 growth factor analog combined with a ceramic scaffold, known as AMPLEX, is currently in a Phase II clinical trial for lumbar interbody fusion in both the US and Canada, where 35 patients are being followed. BioSET has a deal with Biomet Inc. to commercialize B2A for orthopedic use.

Cerapedics Inc. also continues to move forward with i-FACTOR, a technology that incorporates anorganic bone mineral (ABM), a natural hydroxyapatite, with a small amino acid polypeptide (P-15) suspended in a hydrogel carrier. The technology's mechanism of action enhances the natural bone-healing process by promoting the attachment of osteogenic cells. Unlike a bone growth factor such as INFUSE, which promotes ectopic bone, this product only forms bone in sites that produce bone. In April, Cerapedics announced the results of a prospective, randomized, controlled trial of i-FACTORPutty in 1st- and 2nd-level posterior lumbar interbody fusion, showing superiority to autograft with a radiological fusion rate of 98% for i-FACTOR compared to 59% for autograft controls. Patient enrollment is also complete in a randomized, controlled, multicenter prospective Phase III IDE clinical trial at 18 sites evaluating the safety and efficacy of i-FACTOR bone graft in 215 patients with degenerative cervical disc disease. If all goes according to plan, i-FACTOR may be the first approved biologic bone graft for cervical spinal fusion. i-FACTOR was CE marked in 2008 for trauma and spine applications and has since been used clinically in over 3,500 spine, trauma, and orthopedic procedures. It is now commercially available in over 20 countries outside the US.

Kuros Biosurgery AG, a Swiss company, is developing a growth-factor technology based on a parathyroid hormone (PTH) variant. In April, the company regained the rights to three clinical-stage trauma and spinal repair products that were previously licensed to Baxter International Inc. [See Deal] These include KUR-111, a fibrin matrix, variant PTH and hydroxyapatite/calcium phosphate bone graft; KUR-113, a fibrin matrix and a variant PTH, designed to accelerate fracture repair; and KUR-115, in preclinical trials for spinal fusion. Earlier this year, Kuros announced the 12-month results of a Phase IIb trial evaluating KUR-111 for tibial fracture repair. Radiological fracture union was observed in 96.2% of patients treated with low-dose KUR-111, 100% of those treated with high-dose KUR-111, 100% of those treated with autograft

Meanwhile, Pfizer Inc.'s Wyeth, which supplies BMP-2 to Medtronic, is currently in a Phase II IND trial evaluating BMP for treating osteoporosis. In June, Pfizer signed an agreement with CollPlant Ltd., an Israeli developer of Type 1 recombinant collagen derived from tobacco plants, for bone and collagen repair. Also in June, Synthes Inc., in the process of being acquired by Johnson & Johnson (J&J), entered into an exclusive worldwide joint development and licensing agreement with Eli Lilly & Co. to develop site-specific osteoinductive products using Lilly's biologics or pharmaceuticals, including Forteo (teriparatide), an osteoporosis drug for fracture healing. [See Deal] [See Deal] Even so, many of these products are a long way from commercialization in the US.

No Strong Alternative
While there is an assortment of synthetic, composite, allograft, and stem cell products available for use, no one product stands out from the pack. So what are the products that surgeons will likely turn to, if any? In July, BMO Capital Markets completed a survey of 20 spine surgeons and found that the majority (55%) plan to continue to use INFUSE. Of the survey respondents, 44% reported that they would use the product only for approved indications and would not change their usage; while 11% were aware of the risks but comfortable with off-label use in certain indications. However, one-third expected their INFUSE usage to decline between 10% and 30%. The remaining 11% did not use the product. In terms of alternative products, over 60% reported that they would use more allograft or autograft bone, evenly split between the two. (See Exhibit 2.) Now that surgeons are accustomed to using off-the-shelf products, harvesting bone from the iliac crest, while still classified as the gold standard, may be considered a step backward.

EXHIBIT 2
Survey Results: What Alternative To INFUSE Will You Use?

BMO Capital Markets

This, of course, is good news for allograft suppliers such as the Musculoskeletal Transplant Foundation (MTF), LifeNet Health, and AlloSource, which have agreements with most major spine players for both DBM and stem cell products. MTF supplies DBX, the leading DBM product, to Synthes and Trinity Evolution, an allograft stem cell product sold by Orthofix Inc. AlloSource sells DBM through a number of partners, participates in the stem cell arena via a distribution agreement with NuVasive Inc. for Osteocel Plus, and also markets its own product, AlloStem. LifeNet supplies J&J/DePuy Spine Inc. with DBM products; Medtronic markets Osteotech’s line of DBM products; and Integra Life Sciences Holdings Corp., Bacterin International Holdings Inc., and RTI Biologics Inc. all offer a variety of DBM products as strip and sponge configurations sold though strategic partnerships or via their own sales forces. RTI will introduce AthersysInc.’s Multipotent Adult Progenitor Cell (MAPC) technology in the first half of 2012 for the spine, reconstructive, and trauma markets. [See Deal] BioMedGPS believes the $280 million DBM market will be a safe haven for the short term should a fall-out of INFUSE occur, and growth could increase by 10-fold from 2.2% to over 20% as events unfold. Recent checks with allograft suppliers indicate an uptick in sales of allograft DBM products.

Stem Cells Still Unproven

Companies are jumping on the stem cell bandwagon with products derived from
human tissue and most are conducting large-scale trials evaluating their products in multiple spine and orthopedic applications. However, the reality is that stem cell products, such as NuVasive’s Osteocel Plus and Orthofix’s Trinity Evolution - essentially super-charged DBMs that contain residual growth factors harnessed from allograft bone - have yet to be vetted clinically for spine and orthopedic applications and cost as much as INFUSE. Still, interest remains high, even as the FDA begins to closely scrutinize whether or not some products containing living cells, such as Alphatec Spine Inc./Alphatec Holdings Inc.’s PureGen, which utilizes embryonic stem cells from synovial fluid rather than bone marrow, fall under the auspices of a human tissue product. Sales of stem cell products are on track to reach close to $130 million by year’s end, with growth in the 20+% range, according to SmartTRAK projections.

Mesoblast Ltd., a publicly held Australian company, is developing three off-the-shelf products based on a proprietary method of using magnetic beads to extract large quantities of allogeneic adult stem cells, called mesenchymal precursor cells (MPC), from bone marrow aspirate. The company is conducting three Phase II trials for spine fusion (NeoFuse), fracture repair (MPC), and disc regeneration. Unlike other stem cell competitors, Mesoblast is conducting formal IDE trials on its products, which will pay huge rewards should the FDA ever change its stance on human tissue stem cell products.

The US synthetic bone replacement segment is projected to reach about $263 million in sales in 2011 and is expected to deliver robust growth. Those products with bone-forming potential that are approved for posterolateral fusion are likely to be the winners for now. These include Baxter’s Actifuse, obtained via Baxter’s acquisition of ApaTech Ltd, last year, and Stryker’s Vitoss, from the $316 million purchase of Orthovita Inc, in June. [See Deal] In August, Baxter acquired Ceremed Inc.’s Ostene bone hemostasis line of products in an effort to shore up its regenerative medicine business, which was down 10% year/year due to changes in ApaTech’s sales force from a distributor model to primarily a direct sales force. In 2010, Baxter held about 3% of the US bone replacement market. (See Exhibit 3.)

**EXHIBIT 3**

US Bone Market Replacement Market, Share By Supplier

Following the acquisition of Orthovita, Stryker formed a new division, Stryker
Orthobiologics, to centralize the development and marketing of biologics and biomaterial products across Stryker’s operating divisions. Headquartered in the former Orthovita facilities in Malvern, PA, Stryker Orthobiologics is part of the Stryker Orthopaedics division, comprised of the following business units: Hips, Knees, Extremities, Trauma, Craniomaxillofacial (CMF), and Joint Preservation. It is responsible for downstream marketing so that one product can be sold across multiple divisions to tap into the universe of spine, trauma, CMF, and total joint surgeons. Stryker Regenerative Medicine, formerly Stryker Biotech, was created after certain OP-1 products (OP-1 Implant, OP-1 Putty) were divested to Olympus in 2011. This division oversees R&D for growth factor products (OP-1) under development as injectable technologies for disc regeneration and knee osteoarthritis.

The acquisition of Orthovita provided Stryker with a solid portfolio of synthetic bone replacement and hemostasis products. At this year’s American Academy of Orthopaedic Surgeons (AAOS) meeting, the company launched three Vitoss product-line extensions, including the bioactive glass products Vitoss Bioactive, Vitoss Bioactive Foam-2X (which contains higher levels of bioactive glass and has twice the bioactivity of Vitoss Bioactive), and Vitoss BA Bimodal, which is designed to provide a burst release and then a sustained release of silicon ions for increased bioactivity leading to greater calcium phosphate coverage for bone bonding. In addition, a new Bioactive PEEK Cervical Interbody Fusion Device, composed of bioactive glass baked into PEEK (polyether ether ketone) polymer that is designed to enable bone growth into the structural implant, is awaiting 510(k) clearance. CORTOSS, an injectable, nonresorbable, fast-setting glass ceramic polymeric approved for treating vertebral compression fractures will be sold via Stryker Interventional Spine.

To round out its biologic offerings of allografts, DBMs, and synthetics, Stryker entered into an exclusive agreement with RegenLab SA for distribution of the RegenKit-THT, a one-step system designed for safe, rapid preparation of autologous platelet rich protein from a small patient blood sample at the point of care. [See Deal]

Kensey Nash Corp. is also expected to benefit from Stryker's purchase of Orthovita. Kensey and Orthovita had been development partners for over eight years and Stryker's comprehensive distribution network could be a significant growth driver for Kensey's business in 2012. Kensey has signed a number of deals this year, including the acquisition of the orthobiologics product lines of Synthes' Norian Corp, subsidiary for $22 million in cash (the divestiture was mandated as part of a DOJ action). [See Deal] As part of the long-term supply agreement, Kensey will manufacture the Norian products and Synthes will exclusively distribute them worldwide. The companies entered into an R&D agreement as well to create related future products. Earlier this year, Kensey acquired surgical adhesive developer, Nerites Corp., for $20 million cash and made a $5 million minority investment in Orteq Ltd., gaining manufacturing rights to Actifit, Orteq's meniscal implant. [See Deal] [See Deal]

As a result of the Orthovita acquisition, Stryker as well as Alphatec are reportedly winding down distribution agreements with Etex Corp., once the only synthetic supplier with a posterolateral fusion label. Like Stryker, many companies are starting to cross-sell products across multiple divisions. Integra, which acquired spinal hardware company, SeaSpine Inc. for $89 million in an all cash deal, plans to drive penetration of its biologics portfolio across the extremities, orthopedics, neurosurgery, and spine franchises. The most compelling opportunity over the next 18 to 24 months involves sales of bone replacement products by SeaSpine distributors. Also, Integra signed a deal with
Orthofix to distribute a modification of Mozaik, a moldable collagen/beta-tricalcium phosphate bone graft also approved for spinal use, under the brand-name Collage.

Most bone replacement products are indicated for filling voids or gaps (ie, extremities, spine, pelvis, or cranium) not intrinsic to the stability of the bone structure; however, Isto Technologies Inc.’s InQu has a clearance as a bone graft extender in the spine when combined with autograft.

**Implants Will Determine Usage**

When all products are considered equal, the choice of a bone replacement material will likely come down to which manufacturer’s spinal implants are used in a procedure. In its Q1 2012 earnings call, Medtronic acknowledged that the problems with INFUSE had a short-term impact on the firm’s spinal implant business. Taking into account the recent quarterly earnings, those companies experiencing positive spinal implant growth are in a prime position to promote their biologic offerings. Those most likely to see a significant increase in biologic sales are NuVasive, Stryker, Orthofix, and Synthes. However, should spine surgeons restrict INFUSE usage to FDA’s narrow approved indication, ALIF with Medtronic’s LT-Cage, INFUSE sales will plummet. Additional companies that could possibly be hurt by a tightening of off-label INFUSE use are developers of lateral access systems—which are commonly used in conjunction with INFUSE. In fact, that could be a primary reason for the high success rates associated with these procedures.

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Editor’s Note: This article is reprinted from Medtech Insight.