Telephone (312) 236-1600 *Fax (312) 236-0801*

William Blair & Company
Limited Liability Company

222 West Adams Street Chicago, Illinois 60606

OSTEOTECH, INC.

(OSTE)

September 28, 1998 (98-081)
Basic Report

Winton Gibbons (312) 364-8371
wgg@wmblair.com

Price: $28 7/8 ($13 1/8–$32 3/4)
Fiscal Year Ends: December

Fiscal Year	Earnings Per Share	Price/Earnings Ratio
1997	$0.65	44.4x
1998E	$1.02	28.3x
1999E	$1.32	21.9x
2000E	$1.73	16.7x

Earnings Per Share Growth		Return on Equity	
1995-1997	7%	1997	17%
1998E-2000E	30%	1998E	22%

Net Debt/Total Cap. (June 1998):	0%	Dividend:	None
Book Value Per Share (June 1998):	$4.6	Common Shares:	8.7 million
Insider Ownership:	11%	Market Value:	$250 million
Sales (1998E):	$59.7 million		

Investment Opinion: Buy

Osteotech is the world's leading commercial supplier of products to the $790 million potential worldwide market for bone graft material and human (allograft) bone tissue. Approximately 56% of this potential market is in the United States, divided among the market for autografts ($225 million), base allograft bone tissue ($119 million), proprietary allograft bone graft material ($72 million), and synthetics ($25 million). Commercial suppliers such as Osteotech, as well as not-for-profit organizations, process allografts. Osteotech processes donated allograft bone, producing a wide range of products from base allograft bone tissue to its proprietary Grafton® Demineralized Bone Matrix (DBM) putty, gel, and flex products. Osteotech's allograft products currently are sold in the United States through its clients—the American Red Cross Tissue Services (ARC) and the Musculoskeletal Transplant Foundation (MTF)—the largest U.S. bone tissue banks. Grafton® DBM, a high-margin bone graft material, should continue to grow at more than 20% over the next few years, and company margins also should improve as the product mix that Osteotech processes shifts to Grafton® DBM. The company also will enter the fast-growing market for interbody fusion cages with its allograft threaded cortical bone dowels. This market represents an additional $200 million market potential in the United States and $275 million worldwide. Finally, Osteotech will extend its proven business model to Europe, which ultimately should have the same market size as the United States. To build its allograft bone sales in Europe, in June 1998 the company agreed to acquire the majority interest in the French firm, OST Developpement SA. Given these substantial and profitable growth prospects, we recommend purchase of Osteotech shares.

Contents

Summary of Investment Recommendation

Osteotech is the world's leading commercial supplier of products to the $790 million potential worldwide market for bone graft material and human (allograft) bone tissue. In addition, the company will be entering the approximately $275 million market for interbody fusion cages, with its allograft threaded cortical bone dowels (CBDs). Commercial suppliers such as Osteotech, as well as not-for-profit processors, process allografts. The company currently has a 56% share of the nearly $100 million commercial, end-use U.S. market for bone graft material. This market includes proprietary, allograft bone graft material such as Grafton® DBM, as well as synthetic bone graft material. The company also distributes metal medical devices for the spine in the United States and provides hydroxyapatite-coating services to major orthopedics suppliers in Europe.

Our investment recommendation for Osteotech is based on the following four key factors.

- Osteotech is the world's commercial leader in both supplying bone graft material and processing allograft bone, with the combined market for allograft bone, allograft bone graft material, and synthetic bone graft material growing solidly.

- The company's launch of threaded cortical bone dowels used for fusion of vertebrae in the spine provides an exceptional opportunity due the high-demand, fast-growing interbody fusion cage market which currently represents an additional $200 million market potential in the United States and $275 million worldwide.

- Overseas expansion of Osteotech's core services and products, especially into Europe, provides a broad platform for growth that could equal its U.S. position.

- Margins should continue to improve as the company sells more proprietary products such as Grafton® DBM.

Osteotech could have potential EPS upside due to its hydroxyapatite capabilities in the Netherlands through its CAM Implants subsidiary and its U.S. distribution agreement for the metal spinal devices of the German firm Ulrich.

Worldwide Commercial Leader in Both Bone Graft Material and the Processing of Allograft Human Bone

Osteotech has the longest for-profit commercial history, greatest market share, and largest and most-secure donor supply of any processor of allograft bone, allograft bone graft material, or synthetic bone graft material substitute. In March 1987, the company processed it first donor for its first client, the Musculoskeletal Transplant Foundation (MTF). Since then, Osteotech has processed tissue from almost 20,000 donors, providing more than 1.7 million bone tissue transplants. With Grafton® DBM, the company created the bone graft material market in the United States. Currently, Osteotech has a more than 50% market share measured in terms of both sales to the final-end-use customers, such as hospitals, as well as in terms of supplier sales to the clients, such as the MTF, that sell to hospitals. In addition, Osteotech has long-term contracts—5- and 10-year—with the two largest human bone tissue banks, the MTF and the American Red Cross Tissue Services (ARC), which, when combined, account for about 34% of all donors.

Market for Allografts and Bone Graft Material Continues to Grow Rapidly

We estimate that the U.S. market for allografts, proprietary demineralized bone materials (DBM) such as Grafton® DBM, and synthetic bone graft materials should be approximately $216 million total at the end-user level in 1998. Furthermore, we believe that this market will grow at a compounded annual growth rate of just less than 14% through 2003, leading to a market size of about $414 million. The growth in this market is driven by five trends:

1) Underlying population growth

2) A shift in age demographics to an increasing number of individuals more than 45 years old

3) Increases in procedures requiring bone grafts due to technological advancements (e.g., spine-fusion surgeries driven by interbody fusion cages)

4) More surgeries using allografts or synthetic bone graft materials instead of or in addition to the patient's own bone (autograft)

5) Modest price-increases

Threaded Cortical Bone Dowels Provide an Exceptional Growth Opportunity

Threaded cortical bone dowels (CBD) are targeted at one of the fastest-growing medical device segments—interbody fusion cages. Sofamor Danek Group, along with the University of Florida Tissue Bank (UTFB), pioneered the marketing of threaded CBDs—Sofamor Danek's MD product line—as a substitute for metal interbody fusion cages, such as Sulzer Medica Spine-Tech's BAK cage, or Spinal Dynamics' Ray cage. However, Sofamor Danek has been supply-constrained in its ability to sell more CBDs. Osteotech's superior allograft supply position, market position with spinal surgeons afforded to it by its Grafton® DBM franchise, and its 250-person-strong salesforce should enable the company to capture at least a modest share of this market. We estimate sales of $3.5 million in 1999 and $11 million in 2000 for the Osteotech CBDs, primarily in the United States at first, on the basis of the previous penetration of similar competitive products and the dynamics of this market. These revenue projections compare with an overall U.S. cage market size of $200 million in 1998 and between $250 million and $300 million by 2000.

Overseas Expansion of Osteotech's Core Services and Products Should Provide More Growth

The potential for allograft bone and bone graft material in Europe is comparable to that of the total U.S. market size. However, the European allograft bone and bone graft material market still is highly fragmented, with much of the material supplied by local, not-for-profit, hospital-based tissue banks. This should provide Osteotech with an excellent opportunity to expand internationally into Europe, leveraging its proven business model and core bone-processing skills. To take advantage of this opportunity, on June 25, 1998, Osteotech agreed that it would acquire a majority stake in OST Developpement SA (OST), a subsidiary of Transphyto SA, Clermont-Ferrand, France. We believe that incremental Grafton® DBM and allograft sales in Europe should add an additional 10% to the company's total worldwide revenue within six years of its launch.

Margins Should Continue to Improve Significantly

We expect significant continued reductions in cost of sales (COS), selling, general, and administrative expense (SG&A), and research and development (R&D) as a percentage of revenue. While the reduction in COS partly is driven by volume, it mainly is driven by a mix shift to the higher-gross-margin, proprietary products like Grafton® DBM, as well as the reduction in sales of the current European products, which have low gross margins. Grafton® DBM products should constitute 57% of revenue in 1998, compared with 49% in 1997 and 37% in 1996. Also, we forecast that the high-gross-margin products (Grafton® DBM and

CBDs) should make up 62% and 66% of revenue in 1999 and 2000, respectively. Consequently, 1997 gross margin of 65% should increase to 71% by 2000. The SG&A expense ratio also should continue to decline in the future, due to both the leveraging of Osteotech's fixed sales-and-marketing and overhead costs, and the effects of the mix shift mentioned above. By year end 2000, SG&A should have declined about 2% as a percentage of revenue from 1996, mostly due to the product-mix shift, with some contribution from leveraging overhead. R&D expenses have declined in recent years, as the company halted its PolyActive™ polymer program in 1996 due to increased management focus on the core allograft and bone graft material business. We foresee increases slightly less than sales growth from this new base going forward; consequently, R&D should decline as a percentage of revenue, from 8% in 1997 to 7% in 2000.

Financials

Osteotech's financial results should continue to be strong, with significant sales growth, as well as gross margin and operating margin expansion, leading to significant growth in EPS. Company revenue has increased in the double digits since 1990, averaging 30% growth per year through 1997, and we anticipate revenue growth rates of 33% for 1998, and between 23% to 29% for 1999 and 2000 respectively. In addition, we estimate that gross margins will continue to increase, from 65% in 1997 to 71% in 2000. Also, we expect operating expenses to decline from 45% in 1997 to 41% in 2000, raising operating margins from 20% in 1997 to 30% in 2000. The net results of this revenue growth, combined with the improving margins, should be excellent EPS increases of 58%, 29%, and 32% in 1998, 1999, and 2000, respectively.

Risks

Allograft safety (see appendix E). With all transplants of biological material from another human (allografts)—blood, whole organs such as a heart or kidney, or bone—there is some potential for transmission of an infectious disease, such as hepatitis or HIV. However, this risk typically is minimized in two ways. First, the donor is screened for a medical and/or social history that would indicate a potential for high risk. Second, diagnostic tests are performed on the donor (and in the case of blood and bone, the allografts as well) to determine if there is a presence of either an infectious agent or antibodies to an infectious agent. Osteotech adds a third step that ensures product safety—the viral inactivation components of its demineralization process. The first two steps are intended to screen out any allografts that might contain the infectious agent. Osteotech's third step is designed to inactivate a panel of viruses even if it passes through the rigid screens. For example, an HIV virus would have less than a 1-in-2.8-billion chance of passing through the company's proprietary viral inactivation process in samples that had not undergone the first two screening steps. Adding the first two screening steps make the likelihood of transmission orders of magnitude even smaller. Osteotech tracks all donors as single lots and maintains samples of donor material. No confirmed case of any infectious disease transmission or other adverse incident has occurred with the more than 1.7 million units of bone tissue processed by the company that have been transplanted.

Patent litigation with GenSci Regeneration. On January 16, 1998, Osteotech filed a patent-infringement lawsuit against GenSci Regeneration Sciences, which produces DynaGraft Gel and DynaGraft Putty, for violating patent claims Osteotech made in its Grafton® DBM process. In the mid-September, the company also added DePuy—GenSci's marketing partner—to the suit. About two weeks after the January filing, GenSci filed a suit charging that Osteotech violated claims of GenSci patents, as well as for tortuous interference with a business relationship. The GenSci patent suit is targeted at Grafton® DBM flex, which represents only approximately 8% of all Grafton® DBM sales. In addition, the flex matrix defined in the GenSci ("Jefferies") patent claims is made of collagen, which would not apply to Grafton® DBM flex. Lastly, the business with whom Osteotech is accused of interfering is the American Red Cross Tissue Services (ARC). As will be discussed

throughout this report, Osteotech has had an *exclusive* relationship with the ARC since 1988 for processing bone tissue, and it renewed that relationship in 1996 with another 10-year exclusive agreement. Consequently, we see little merit in either of the GenSci claims, although patent litigation is difficult to predict. Both suits currently are in the discovery phase and should go to trial within a year.

University of Florida/Regeneration Technologies Patent for Threaded Cortical Bone Dowels. At the end of August, Regeneration Technologies, Inc., the for-profit development spin-off from the University of Florida Tissue Bank (UFTB), was issued U.S. Patent No. 5,795,352, which covers the manufacturing and use of the threaded MD threaded cortical bone dowel—the one marketed by Sofamor Danek Group. At this point, there appears to be no major reason for concern regarding the claims in this patent when compared with the threaded cortical bone dowel and manufacturing process currently under development by Osteotech.

Regulatory (see appendices C and D). Human tissue is subject to various government regulation in most countries. Consequently, Osteotech's success in part depends on its ability to obtain and maintain the required regulatory approvals. In the United States, the company is subject to two types of regulation—those involved in the safety of the products (e.g., the Food and Drug Administration [FDA]), and those related to the procurement and distribution of human organs and tissue (e.g., U.S. National Organ Transplant Act [NOTA]). In addition, it will be subject to European regulations in the near future as it enters that market. In the United States, Osteotech's allograft bone products are regulated as human tissue for FDA purposes, and not as medical devices. Even Grafton® DBM was designated as human tissue by the FDA in August 1995. Recently, the FDA has released a new proposed rule to regulate human tissue-based and cellular-based products comprehensively. Under this proposed rule, it appears that Grafton® DBM still would be regulated as the least-restrictive (i.e., minimally manipulated) human tissue. Under NOTA, the sale of human organs and tissue is strictly prohibited, but service fees may be charged by all parties involved, including third-party processors like Osteotech. Thus, in order to ensure an adequate and safe supply of human tissue for transplant, service fees are allowed and typically levied to procure, transport, process and store tissue. These fees allow the parties involved to invest and receive a return on capital in order to improve tissue safety—for example through better screening and testing, increase the supply of tissue—for example through process yield improvements, and improve the properties of tissue—for example by developing proprietary products. As discussed in appendix D, European regulations appear to be developing in a manner similar to U.S. regulations.

The Company

From its 1986 founding to the present day, Osteotech has continued to lead the human allograft bone tissue processing and bone graft material markets. As table 1 illustrates, the company has built and maintained relationships with the two largest bone tissue banks in the United States. In addition, the company has built on allograft bone tissue processing to develop its proprietary products, such as its Grafton® DBM line. To secure its leadership position, Osteotech maintains a large, competitive sales effort and has maintained its focus on leveraging its core human allograft tissue-processing technology as its growth engine for the past several years.

Table 1
Osteotech, Inc.
Timeline

February 1986	Osteotech incorporated
March 1987	Processes first donor for first client, MTF
August 1988	ARC names Osteotech as its exclusive bone allograft processor
September 1988	The Eurotransplant Foundation—Europe's largest transplant organization—becomes Osteotech's first international client
November 1989	Opens dedicated demineralization-processing lab
September 1990	AATB accredits Osteotech's asceptic bone tissue process
July 1991	IPO
August 1991	Grafton® gel introduced (only distributed by MTF)
December 1991	Awarded a patent for Grafton® formulations (#5,073,373)
May 1992	Acquires HC Implants, BV in the Netherlands
June 1993	Acquires distribution rights to spine implants made by the German firm Heinrich C. Ulrich, KG
August 1995	FDA designates Grafton® as human tissue
Late 1995	ARC begins distribution of Grafton® products
January 1996	Grafton® flex introduced
March 1996	Processes 1 millionth unit of human bone tissue
October 1996	Discontinues PolyActive™ polymer R&D program
November 1996	Grafton® putty introduced
December 1996	Signs 10-year exclusive agreement with ARC for allograft bone tissue
April 1997	Signs 5-year exclusive agreement with MTF for allograft bone tissue
November 1997	Signs long-term agreement to supply ConvaTec with hydroxyapatite granules for its urethral sphincter augmentation device
June 1998	Acquires 5% of OST Development, SA in France with an option to purchase the entire firm

Source: Company data; William Blair & Company, L.L.C. analysis

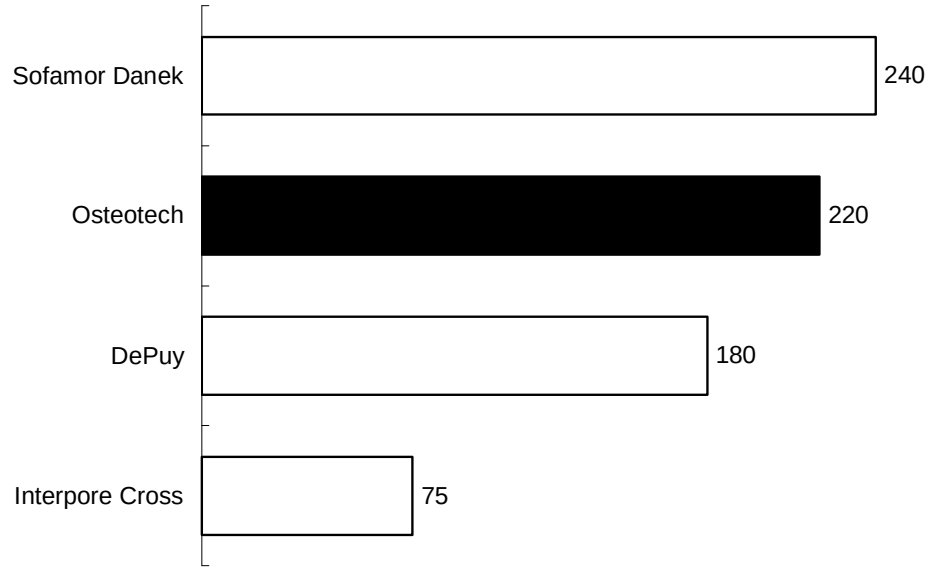
Osteotech provides human bone processing services to the two largest U.S. tissue banks under exclusive agreements. Osteotech was incorporated in February 1986 with the intention of processing allograft bone for tissue banks. This bone tissue originally consisted of processed bone sections and pieces, as well as dry, ground demineralized bone material (DBM), all of which will be referred to as base allograft in this report. In March 1987, the company processed its first donor for its first client, the aforementioned Musculoskeletal Transplant Foundation (MTF). To facilitate the donation of bone, the company helped in the formation of the MTF, its first and largest client. The MTF originally was made up of various organ-procurement organizations, tissue banks, and academic medical institutions. Currently, the MTF is the largest U.S. bone tissue procurement organization, with approximately 2,400 donors estimated in 1998. In addition to MTF, Osteotech signed an agreement with the American Red Cross Tissue Services (ARC) in August 1988 to become the ARC's exclusive processor of bone tissue. The ARC is the nation's second-largest bone tissue bank, with about 1,600 donors estimated in 1998. Since then, the company has renewed its long-term agreements with these clients. A new 10-year agreement was signed with ARC in December 1996, and a new 5-year agreement was signed with MTF in April 1997. Appendix C discusses the donor procurement and allograft bone distribution processes in more detail.

Osteotech is adding proprietary products to increase revenue and margins. In August 1991, Osteotech introduced Grafton® DBM gel, a suspension of DBM in glycerol, an inert agent (excipient) that provided better handling characteristics than DBM alone. In December 1991, the company also was granted its first patent covering Grafton® DBM formulations. Grafton® DBM, as a proprietary product with unique and desired features and benefits, became Osteotech's engine for both revenue and margin growth. At first, only MTF carried Grafton® DBM, but in late 1995 the ARC began to distribute it as well. In 1996, Osteotech expanded the Grafton® DBM product line with Grafton® DBM flex, a formulation that formed a flexible strip, and Grafton® DBM putty, a formulation, as its name implies, that allows the surgeon to mold the product to fit the needs of the particular site and type of surgery.

Osteotech soon will launch threaded cortical bone dowels to compete in the interbody fusion cage market. Surgeons have shown a great reception for similar products from Sofamor Danek, but this company and its partner, the UFTB, have been donor-supply constrained. This situation should provide Osteotech an exceptional opportunity given its significant donor-supply advantage.

Osteotech has a strong sales organization. Osteotech uses 57 independent sales agencies, supported by its own 21-person field-marketing organization to promote its proprietary products, such as Grafton® DBM. As shown in figure 1, the resulting 230-person sales-agent salesforce size is tantamount to the two largest spine competitors, Sofamor Danek and DePuy Motech/AcroMed, and actually exceeds that of DePuy by up to 40 representatives. As we discuss later in this report, these spine competitors are forming the primary new competition for bone graft material, and Osteotech's comparably sized salesforce should continue to allow it to compete well. As figure 1 also shows, Osteotech's salesforce is roughly 3 times larger than the strongest synthetic bone material supplier, Interpore. Besides size, the Osteotech salesforce also has advantages in training, experience and focus. Its sales agents have been marketing these bone graft material products far longer than any other agents, and the agent representatives have received continued and extensive training in bone tissue science. In addition to the company's Grafton® DBM salesforce, the MTF and ARC maintain their own sales efforts for the base allograft.

Figure 1
Osteotech, Inc.
Competitive U.S. Salesforce Sizes



Source: Company interviews; William Blair & Company, L.L.C. estimates

Current Osteotech senior leadership brings deep orthopedic and health care experience and understanding, leading to a focus on proprietary allograft products. All members of the senior management team have extensive experience in either orthopedics or other health care firms. For example, Roger Stikeleather, executive vice president of Sales was vice president of Sales for the Extended Care Products subsidiary of Johnson & Johnson, and James Russell, executive vice president of Research & Development was a director of Research for the Pharmaceutical Division of Proctor & Gamble. Michael Jeffries, COO and CFO, has been with Osteotech nine years and was with various health care organizations prior to arrival. Richard Bauer, the president and CEO, has the most extensive orthopedics experience. Specifically, Mr. Bauer joined Osteotech as president and CEO in February 1994. Just before joining the company, he had been president of the Prosthetic Implant division of Zimmer, a subsidiary of Bristol-Myers Squibb and the largest orthopedics company in the world. Mr. Bauer also had served as general manager of Zimmer's Fracture Management division and as vice president of marketing for its Orthopaedic Implant division, giving him considerable breadth and depth in the entire orthopedics business. Once at Osteotech, Mr. Bauer used his understanding and sophistication to refocus the company's business to its core strengths in allograft processing and the development of proprietary allograft products, where considerable market demand still exists. As mentioned above, Osteotech introduced two new Grafton® DBM products in 1996 and is developing a proprietary allograft threaded cortical bone dowel. In addition, Mr. Bauer and his senior management team are leading Osteotech to Europe, where it can leverage its proven business model, through its recently announced acquisition of OST. To maintain this focus, Mr. Bauer also discontinued the company's PolyActive™ polymer research and development in at the end of 1996, keeping most current R&D focused on human allograft bone tissue. Also, to leverage nonallograft assets acquired before his tenure, Mr. Bauer has signed a long-term OEM agreement to supply ConvaTec with hydroxyapatite particles that the company will use in its urethral sphincter augmentation device. Currently, Osteotech senior management owns approximately 11 percent of the shares of the company, including stock options. Both the cash bonus and stock option program are tied directly to increases in net income.

The Market for Allograft Bone and Bone Graft Materials

Allograft Bone and Bone Graft Materials Fill Important Medical Needs

As shown in table 2, on the next page, allograft bone and bone graft materials are used in a variety of indications, either to replace bone or for bone growth. Spinal fusion is the largest market, accounting for approximately 45% of procedures, followed by various maxillofacial procedures, which constitute 14% of the total. In addition, other orthopedic procedures require these materials, such as the removal of bone tumors (9%) and various fracture repairs (16%-24%).

Table 2
Osteotech, Inc.
Major Uses of Bone Grafts

Indication	Requirement	Percentage of U.S. Bone Grafts
Spine fusion	Almost all	45%
Maxillofacial	Depends on type of surgery (e.g., orthonathy, endosseous implants)	14%
Bone tumors	Most	9%
Nonunion fractures	70%	8%
Trauma/Emergency	65%	8%
Tibial plateau fractures	15%	8%
Hip fractures	10%	8%
Total hip revisions	15%	3%
Other	--	5%

Source: MDI; Osteotech, Inc. ; NCHS; industry interviews; William Blair & Company, L.L.C. analysis

When possible, surgeons often employ the patient's own bone (i.e., autogenous bone graft) harvested at the surgical site, or from another site, usually from the top of the hip (iliac crest), ribs, or chin. Using autogenous bone graft is considered the "gold standard"; however, there often are considerable problems with using autograft. Potential problems with the use of autogenous bone fall into four categories: autograft failure, donor-site morbidity, insufficient donor material, and metabolic hindrances for individual patients. First, the autograft fails up to 35% of the time—i.e., not achieving the necessary bone growth—even with some form of fixation device. Second, if one must harvest the patient's own bone from the iliac crest, this requires a second surgery, as well as the associated cost and time. Also, in perhaps 25%-30% of cases, there is pain or other morbidity at the donor site. Some patients who have had surgery complain that the donor-site pain is worse than the original pain for which they were treated. Third, there may not be enough donor material, due either to previous graft harvests, the patient's needing more tissue than is available from his own body (for example, in the case of a multilevel spine fusion or removal of a large tumor), or simply that the patient's own bone quality is insufficient, which is especially true in older individuals. Fourth, individual patients may have other conditions that can slow down or prevent fusion, including smoking, osteoporosis, or diabetes.

To address these shortcomings, surgeons use base-allograft transplants, demineralized bone material such as Grafton® DBM, synthetic bone graft materials, and other bone growth stimulators. A variety of approaches have been and are under development. These can be divided into six groups: human allografts (such as those supplied by Osteotech), processed bone from animals (xenografts), synthetic grafts, bone growth factors, electrical stimulation, or ultrasound. More details are discussed regarding this variety of materials in the following section concerning Osteotech's market position, as well as in appendix B.

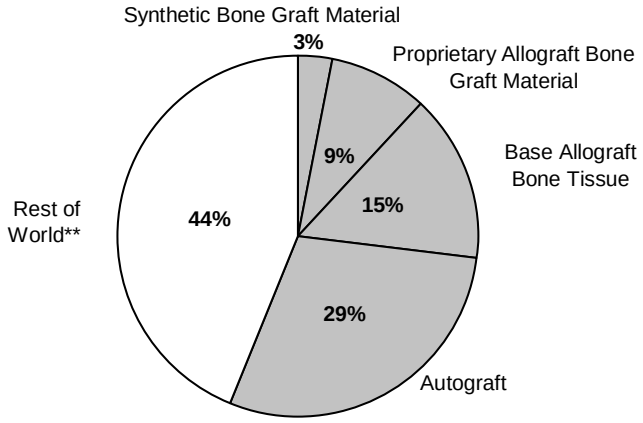
Allograft Bone and Bone Graft Materials Market Growing Rapidly, with Substantial Potential of Almost $800 Million

Figure 2 shows the components of the $790 million worldwide market for bone grafts. As one can see, approximately 56% of this potential market is in the United States, divided among the market for autografts ($225 million), base allograft bone tissue ($119 million), proprietary allograft bone graft material ($72 million), and synthetics ($25 million). Figure 3

shows our estimates of the U.S. market sizes for nonautograft products from 1997 to 2003. As can be seen in both figures 2 and 3, the current market size for nonautograft products is about $216 million, compared with a potential total U.S. market including autograft of $440 million. We estimate that the U.S. nonautograft market is growing at just less than 14% annually, which should lead to a market size of almost $415 million by 2003. This growth is driven by the aforementioned five trends: underlying population growth; a shift in age demographics to an increasing proportion of individuals more than 45 years old; increases in procedures requiring bone grafts due to technological advancements (e.g., spine-fusion surgeries driven by interbody fusion cages); more surgeries using allografts or synthetic bone graft materials instead of or in addition to the patient's own bone (autograft); and modest price increases.

Figure 2
Osteotech, Inc.
1998 Potential Worldwide Market for Bone Grafts*

100% = $790 Million

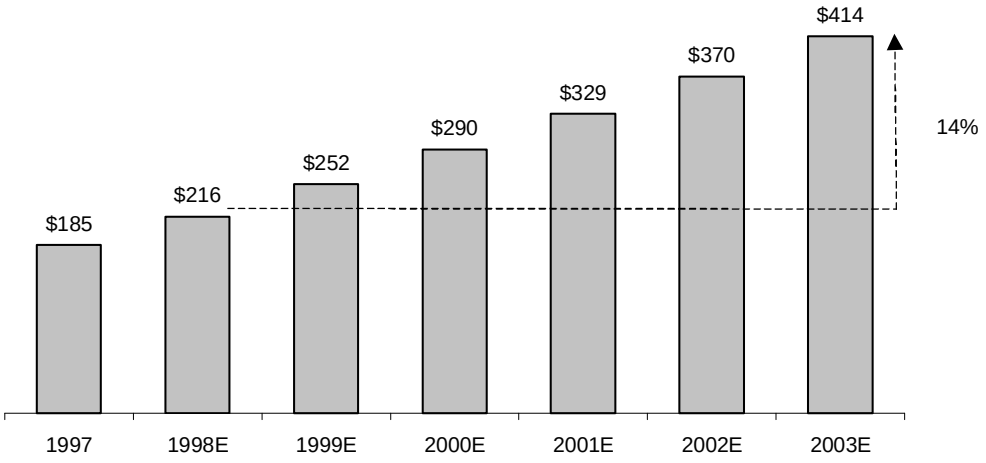


* Does not include cortical bone dowels (part of the fusion cage market)
** Autograft, with some hospital-based allograft

U.S. Market

Source: Various company financials; MTF; ARC; AATB; other tissue banks; National Center for Health Statistics; U.S. Census; industry interviews; William Blair & Company, L.L.C. estimates

Figure 3
Osteotech, Inc.
Total End-use Market for Allograft, DBM, and Other Bone Graft Materials*
($ in millions)

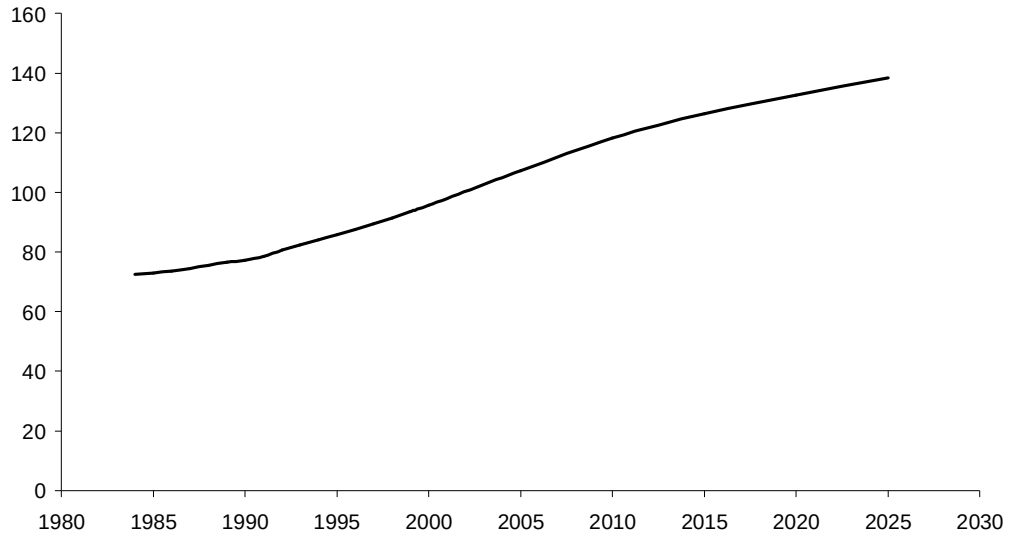


* Excludes periodontal/dental

Source: Various company financials; MTF; ARC; AATB; other tissue banks; National Center for Health Statistics; U.S. Census; industry interviews; William Blair & Company, L.L.C. estimates

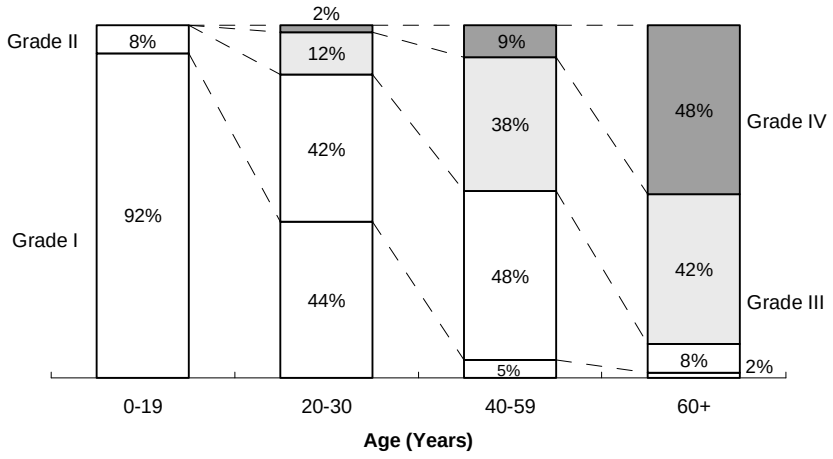
The total U.S. population is growing by about 2.3 million people per year, with an attendant increase in underlying medical procedures. In addition, the U.S. population 45 years old and older is growing, leading to more medical procedures specific to that age group that require bone grafts. As shown in figure 4, we estimate that this population will increase by 20% between 1997 and 2005, from 90 million to 107 million. These older individuals will require more procedures, such as spinal fusion due to disc degeneration, than the overall population. For example, as figure 5 illustrates, spinal-disc degeneration is significant after age 40, with 47% of individuals having some grade III and IV degeneration for those in the 40-60 age group, and 90% having some grade III and IV degeneration in the over-60 age group. Also, the site of fractures changes for older people, and as shown in figure 6, 54% of bone fractures in individuals over 65 occur in the hip, with at least 10% of these hip fractures requiring a bone graft.

Figure 4
Osteotech, Inc.
Estimated U.S. Population More Than 45 Years Old
(millions)



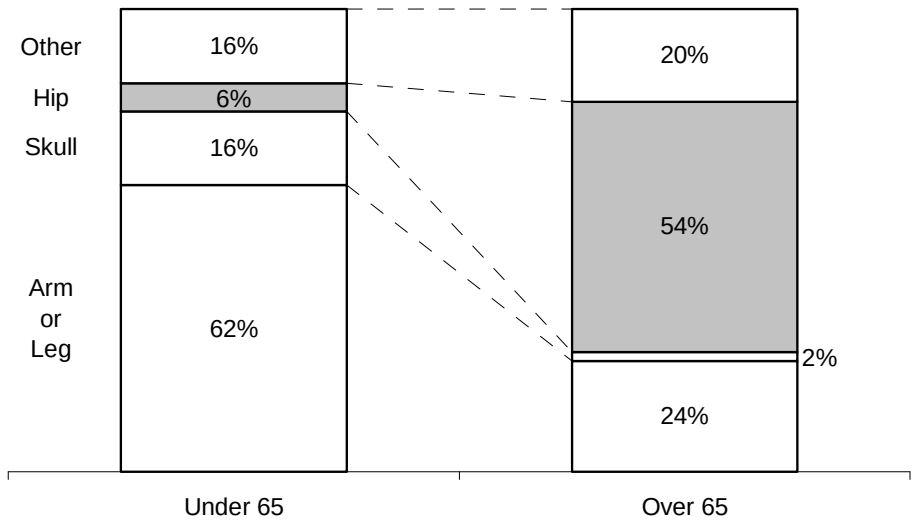
Source: U.S. Census Bureau; William Blair & Company, L.L.C. analysis

Figure 5
Osteotech, Inc.
Effect of Aging on Lumbar Disc Degeneration*



* Grade I (least-degenerated); Grade IV (most-degenerated) (see glossary for details)
Source: *Spine*; William Blair & Company, L.L.C. estimates

Figure 6
Osteotech, Inc.
Sites of Fractures



Source: NCHS; FDA; William Blair & Company, L.L.C. estimates

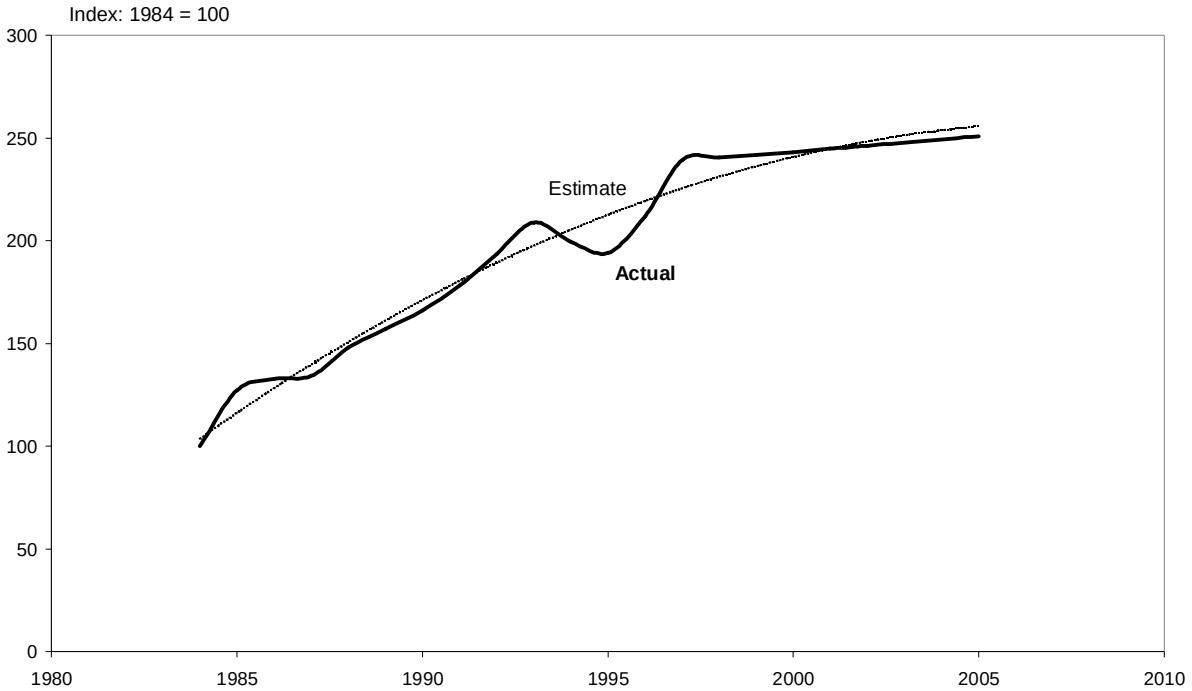
Three other trends are driving the growth of bone-related allografts or synthetic grafts: increased procedure volume due to medical improvements, growing use of nonautogenous grafts, and modest price increases. As mentioned, spinal fusion is one of the major uses of bone grafts, and spinal-fusion rates continue to rise due to the fact that total cost and burden of spinal disorders are strong qualitative drivers of growth. As table 3, on the next page, illustrates, spine conditions and injuries are common, disruptive, and costly. Businesses and government want to reduce lost work time and other costs associated with spine-related disabilities, which total at least $100 billion annually worldwide for back pain alone. In addition, patients want to eliminate chronic pain and loss of function. Consequently, payors, physicians, and patients all have vested interest, as well as financial incentives, to treat these illnesses. All of these factors are leading to increased spinal-fusion rates, as shown in figure 7, on the following page. As mentioned, there are significant potential problems with using autograft, and this has meant a growing use of other grafting materials to either replace or extend the autograft. We expect this trend to continue, with other grafting materials capturing an incremental 2% per year of the overall market for at least the next five years. Lastly, over the past few years, bone graft suppliers have been able to increase prices by 5%-10% per year, as these products are physician-preference items, meaning that the surgeon makes the buying decision, typically on features other than price. We expect these price increases to continue, but moderating to a level of no more than 5% per year.

Table 3
Osteotech, Inc.
Total Effects and Costs of Spinal Conditions

- At least $100 billion total worldwide cost for back pain alone
- Most-common medical complaint (back pain) in the United States
- Second-most-common reason for being absent from work after the common cold
- 100 million lost work days in the United States
- Most-common cause of disability for under age 45 in the United States
- More than 15 million spine-related visits annually to physician offices, emergency rooms, or outpatient clinics in the United States
- Four out of five adults will experience significant back pain during their lives

Source: AAOS; NASS; *Spine*; New England Journal of Medicine; American Journal of Public Health; *Safety & Health*; *Business & Health*; National Center for Health Statistics; U.S. Census Bureau; Agency for Health Care Policy and Research; William Blair & Company, L.L.C. analysis

Figure 7
Osteotech, Inc.
Spinal Fusion Rates



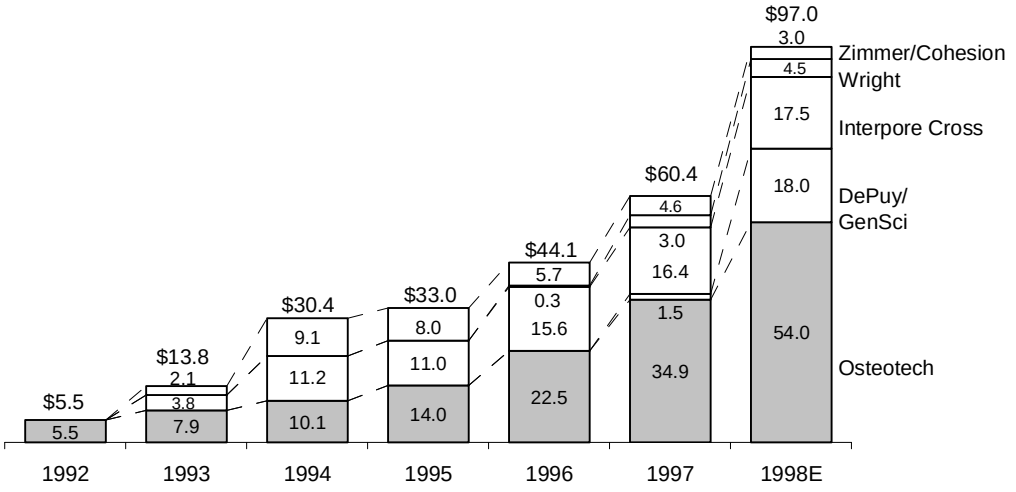
Source: Various company financials; National Center for Health Statistics; U.S. Census Bureau; MDI; MarketLine; Theta; Frost & Sullivan; Dun & Bradstreet; Industry Interviews; William Blair & Company, L.L.C. analysis

Osteotech's Market Position

Market Size and Shares

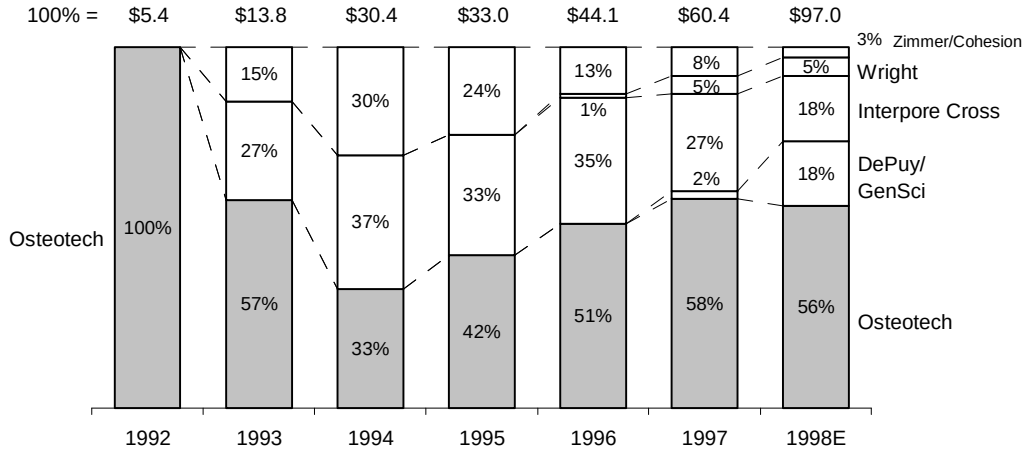
As mentioned, the total worldwide end-use market potential for bone grating products is approximately $790 million, $440 million of which is in the United States. In 1998, we estimate that the actual end-use market for allografts and synthetic grafts is almost $216 million (as shown in figure 3) and growing at almost 14% per year. This market is divided into the base allograft market, the proprietary allograft bone graft material market, and the synthetic market. We estimate that the current end-use market for bone graft material alone that is driven by commercial, proprietary allograft bone graft material and synthetic graft suppliers will be almost $100 million of the total, as shown in figure 8. By year end 1998, Osteotech should have by far the largest share, with 56% of the end-use market, followed the DePuy/GenSci combination and Interpore, both forecast to be 18% by year-end (see figure 9).

Figure 8
Osteotech, Inc.
U.S. Commercial Bone Graft Material End-User Sales
($ in millions)



Source: Company financials; Interviews; MDI; William Blair & Company, L.L.C. estimates

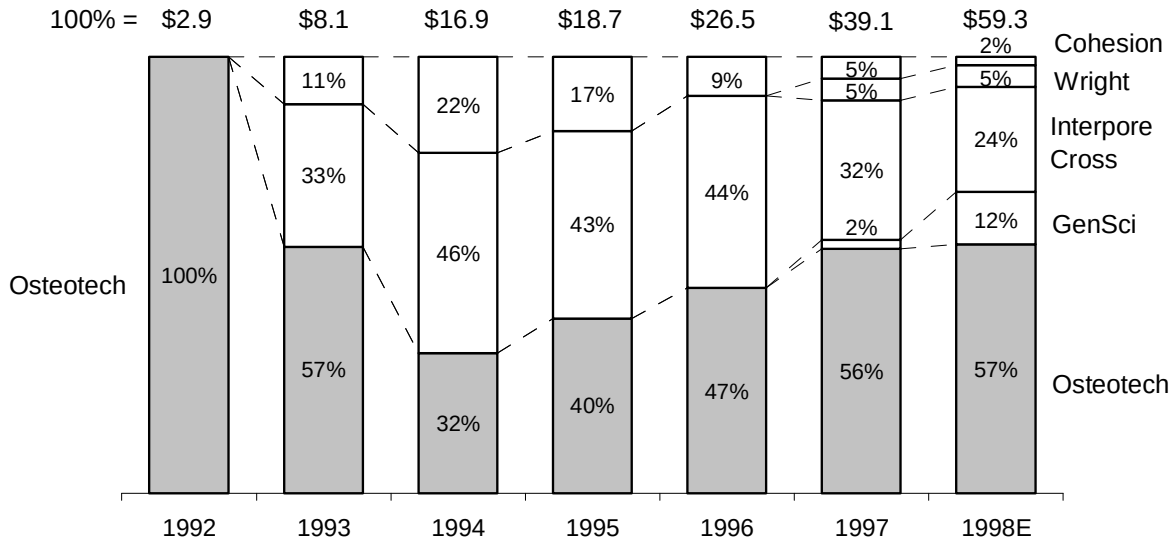
Figure 9
Osteotech, Inc.
End-use Market Shares
($ in millions)



Source: Company financials; Interviews; MDI; William Blair & Company, L.L.C. estimates

Of the estimated almost $100 million in end-user bone graft material revenue generated by the commercial allograft and the synthetic suppliers, only about $60 million is captured at the supplier level, as shown in figure 10. This is due to the various marketing and reselling arrangements that permeate the industry. Obviously, Osteotech must share its fee revenue with the MTF and ARC. In addition, GenSci must share its fee revenue with DPU, as well as its tissue banks, and Cohesion Technologies must share its synthetic graft revenue with Zimmer, its marketing partner. Even Interpore and Wright Medical must share 20%-30% of their revenue with their agents or distributors. These relationships are critical for understanding where value is being captured. For instance, if we examine Osteotech's end-use revenue, it should decline modestly, from 58% in 1997 to 56% in 1998, but its share of the supplier revenue should still remain a commanding 56-57%. Also, we see that while GenSci should capture 21% of the end-use market in 1998, it most likely will capture only 14% of the supplier revenue.

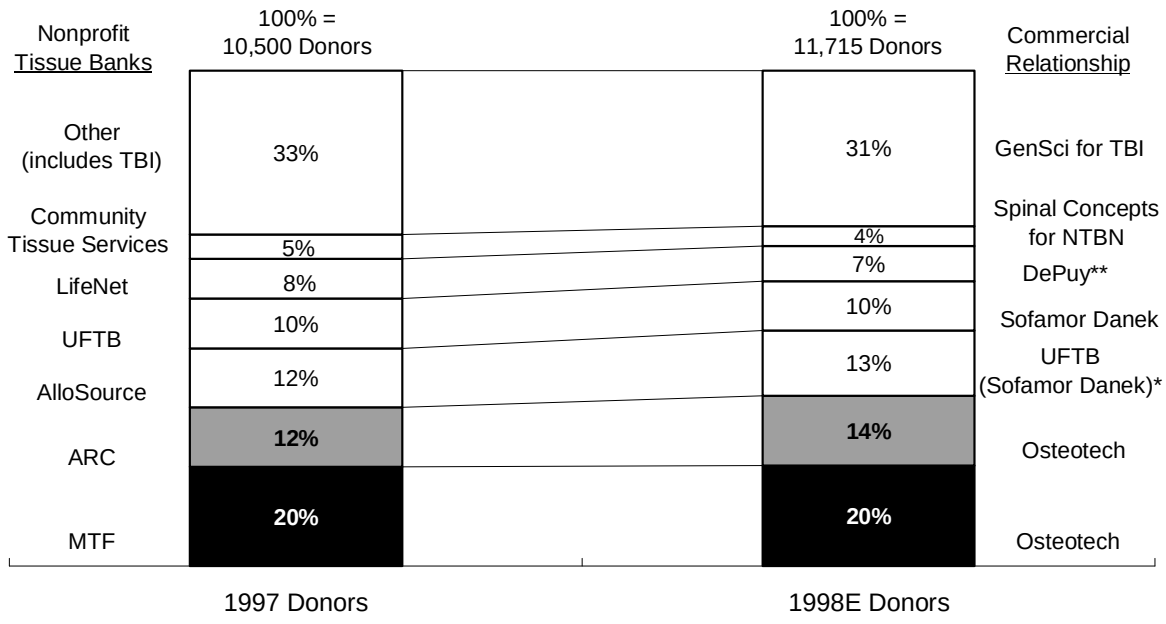
Figure 10
Osteotech, Inc.
Supplier Revenue Market Shares
($ in millions)



Source: Company financials; Interviews; MDI; William Blair & Company, L.L.C. estimates

We are also seeing a shift of revenue away from the not-for-profit market as tissue banks line up with commercial suppliers, more-proprietary allografts are sold, and synthetic materials make modest market penetration. For example, while we estimate the total market to have risen by about 18% from 1997 to 1998, we estimate that the supplier revenue rose 54%. As mentioned, the tissue banks are aligning themselves with commercial organizations through marketing and processing arrangements. Figure 11 shows that all of the largest tissue banks have recently made commercial arrangements—University of Florida Tissue Bank, and through it, AlloSource, with Sofamor Danek; TBI, through GenSci; and LifeNet, with DePuy. We should reemphasize that as figure 11 demonstrates, Osteotech has long-term contracts with the two largest tissue banks, capturing 34% of the donor supply.

Figure 11
Osteotech, Inc.
Annual Bone Donors



* Femurs only for cortical bone dowels

** GenSci has separate agreement for making DynaGraft

Source: Tissue banks; AATB; MDI; William Blair & Company, L.L.C. estimates

Product Comparisons for Bone Graft Materials

There are three dimensions on which surgeons judge bone graft materials: efficacy in bone growth, handling characteristics, and perception of safety. In addition, for investment purposes, one also must assess the regulatory framework governing a particular product. On the next page, table 4 summarizes the commercially available bone graft materials, and table 5 outlines the bone growth properties of the various bone graft materials, both those commercially available and in development.

Bone growth properties. As table 5 illustrates, only autograft, which is derived from the patient's own bone provides bone-forming (osteogenic) cells, causes bone cells to differentiate and grow (osteoinductive), and provides a scaffolding upon which the bone can grow (osteoconductive). This table also demonstrates that only naturally derived bone graft materials, such as Grafton® DBM, which is made from demineralized bone matrix, impart both osteoinductive and osteoconductive properties. The synthetic materials, such as ProOsteon (hydroxyapatite) from Interpore, and OsteoSet (calcium sulfate) from Wright Medical, only have osteoconductive capabilities. We believe that this is, in part, what has limited the synthetics' market penetration and sales growth, as shown in figure 8.

Handling. The other property makes Grafton® DBM favorable to current synthetics is handling. As shown in table 4, Grafton® DBM comes in a variety of forms—gel, putty and flex—with the putty form being the overall preferred product, because it is easy to handle and mold as necessary during surgery. In contrast, ProOsteon and OsteoSet are in granular or pellet forms that do not stick together well and are not easily molded, reducing their acceptance by surgeons.

Table 4
Osteotech, Inc.
Summary of Commercially Available Bone Graft Materials

Product	Supplier	Composition	FDA Process	Available Forms	Price per CC
Grafton®	Osteotech	Demineralized bone material (DBM) in a glycerol carrier	Human Tissue	Gel	$75
				Putty	$80
				Flex	$77
DynaGraft®	GenSci	DBM	Human Tissue	Gel	$76*
				Putty	$72*
				Matrix	$70*
ProOsteon®	Interpore	Hydroxyapatite	PMA	Blocks	$90
				Granules	$24**
OsteoSet®	Wright Medical	Calcium sulfate	510(K)	Pellets	$22**
Collagraft®	Cohesion Technologies	Collagen, hydroxyapatite, tricalcium phosphate	PMA	Paste	$97
				Strips	$92

* After October 1998 price increase of 9%

** Allograft cancellous chips = $11

Source: *Spine*; Company financial filings and products brochures; FDA; *U.S. Federal Register*; MDI; William Blair & Company, L..L..C. analysis

Table 5
Osteotech, Inc.
Bone Growth Properties of Bone Graft Materials

	Type of Material	Osteoconductive	Osteoinductive	Osteogenic
Autograft	Natural	√	√	√
Allograft	Natural	√	√	
Demineralized Bone Matrix (DBM)	Natural	√	√	
Xenograft	Natural	√	√	
Bioglass	Synthetic	√	√*	
Hydroxyapatite	Synthetic	√		
PGA / PLA polymer	Synthetic	√		
Collagen	Synthetic / Natural	√		
Calcium sulfate	Synthetic	√		
Calcium phosphate	Synthetic	√		

* Some data indicates osteoinductivity

Source: *Spine*; MDI; Interviews; William Blair & Company, L.L.C. analysis

Safety. The last feature considered by surgeons is safety. Synthetic manufacturers promote the impossibility of infectious-disease transfer, often these products' most important attribute. As we discuss in detail in appendix E, the safety of Osteotech's allograft products is well-documented and preserved through strict screening procedures, as well as a validated viral-inactivation process. On the basis of historical market penetration and revenue growth, as well as discussions with surgeons, we conclude that the safety of the Grafton® DBM product line is well-accepted and that the other features mentioned previously therefore are more important in the buying decision.

Another consideration regarding safety is the carrier or matrix that may be used to modify a bone graft material's handling characteristics, for example to make a putty. Osteotech uses glycerol for Grafton® DBM. Glycerol occurs naturally in some foods, as well as beer and wine, and also is added to a wide variety of foods, ointments, juices and syrups, in addition to medications like cough medicines and mouthwashes. It is classified as a multiple-purpose food substance. This contrasts with other potential carriers such as bovine collagen, which is used in Collagraft. Bovine collagen may cause an adverse response in people with sensitivity to beef, with severe allergies, or those with inflammation involving bone (osteomyelitis).

FDA regulations. From an investment standpoint, it is important to understand the FDA regulatory framework used to approve a product; this is especially important for products in development. Appendix D discusses this issue in detail for human tissue. The most important points are: 1) minimally manipulated human tissue such as Grafton® DBM only should be subject to infectious disease screening and good tissue practices, but requires no premarketing review; and 2) any human tissue that is combined with a noncellular or nonallograft component, such as collagen, generally should require a PMA, the longer medical-device approval process. For synthetics, the environment also appears to be evolving. Before launch, Interpore faced a PMA process for ProOsteon, as did Cohesion Technologies with Collagraft. However, Wright Medical was able to use a 510(k) process (the shorter process for medical devices) for OsteoSet, as it was able to identify a similar product already marketed before 1976, the cutoff year for a 510(k) predicate device. We expect this synthetic area to evolve, due in large part to the FDA Modernization Act of 1997, which resulted in more products being approved through a modified 510(k) process (including limited human data) if used as bone void fillers, but requiring a PMA if used in the spine, which possibly was linked with the specific instrumentation used.

Developmental products. Table 6 shows the competitive products in the pipeline, as well as the likely FDA processes. As shown, there are many synthetic products and materials in development. The major driving force behind these developments is to improve the handling characteristics versus current synthetics on the market, as well as the body's ability to resorb the products during the bone remodeling process. However, by themselves, *none of these new synthetic products will be osteoinductive*, limiting their use even if handling is improved. Thus, we believe that they essentially will be competing for the 26% of the end-use market that is currently captured by synthetic suppliers such as Interpore Cross, Wright Medical and Cohesion Technologies, as shown in figure 9.

Table 6
Osteotech, Inc.
Developmental Bone Graft Materials

Product	Supplier	Composition	Anticipated FDA Process	Available Forms	Comments
Osteofil™	Sofamor Danek	DBM in a collagen carrier	PMA (due to collagen carrier)	Paste	Supplied by UFTB / RTI
embarc™	ETEX	Calcium phosphate (α-BSM)	510(K)*	Paste Putty	Biomet is marketing partner Approved for dental
IMMIX™	Osteobiologics	PGA / PLA polymer	510(K)*	Blocks Granules	
Osteoglass®	U.S. Biomaterials	Bioglass	510(K)*	Fine granules	Approved for dental
SRS®	Norian	Calcium phosphate, calcium carbonate and sodium phosphate	PMA	Paste	For fracture repair
Healos®	Orquest	Calcium phosphate on collagen carrier	PMA	Paste Strips	Clinical trials ongoing with SM Spine-Tech

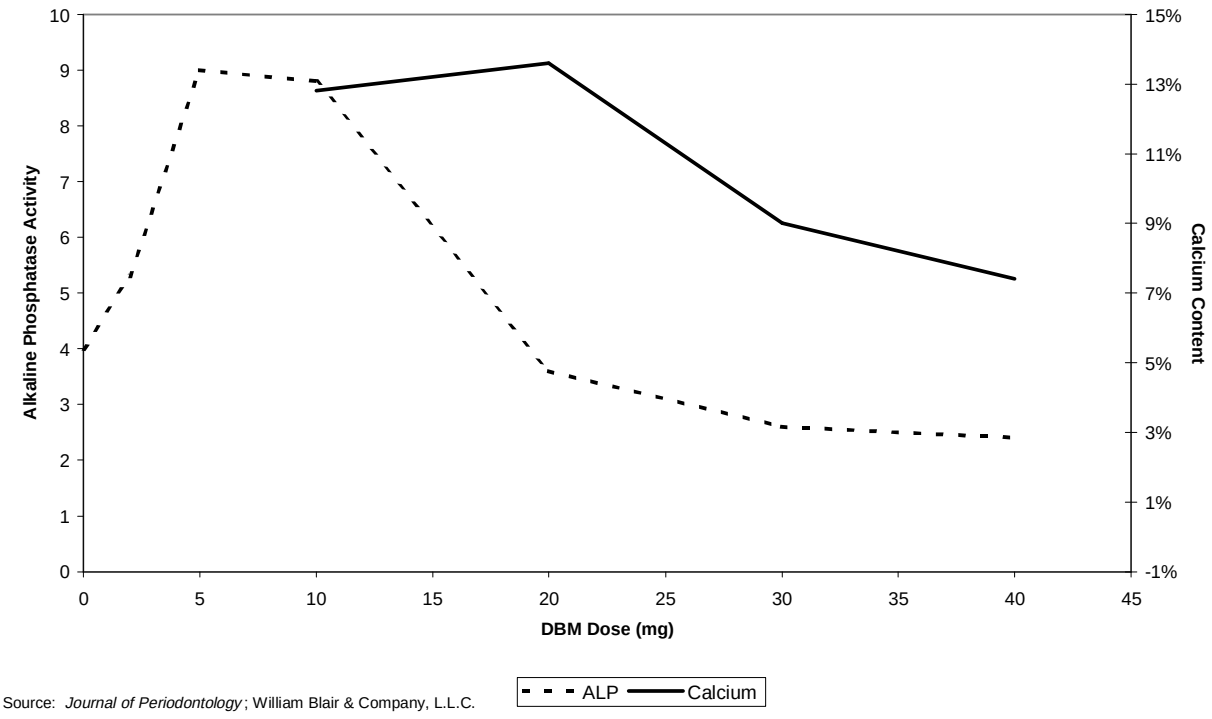
* Including limited human trials

Source: *Spine*; Company financial filings and products brochures; FDA; *U.S. Federal Register*; MDI; William Blair & Company, L.L.C. analysis

Efficacy of Various DBM Products

Some of Osteotech's competitors claim that their DBM products either are more effective because of they contain a higher percentage of DBM per carrier than a mixed product like Grafton® DBM or the different processing used to make their DBM. As shown in figure 12, there is a dose response to the DBM content that declines at higher doses or concentrations. In other words, as measured by two proxies for bone cells differentiation and growth—alkaline phosphatase activity and calcium content—as implanted DBM content increases, there is first an increase in the two proxies then a noticeable decrease. Thus, packing more DBM into a carrier may not only not improve efficacy, but may actually degrade it. Indeed, in the April 15, 1998 issue of the medical journal *Spine,* a study that compared various cervical fusion devices, but controlled for different graft material, showed no difference between Grafton® DBM and autograft, the "gold standard." Furthermore, regarding the efficacy of various DBMs on the basis of sterilization technique, recent histological studies comparing Grafton® DBM with DynaGraft show that while Grafton® DBM induces new bone formation, it appears that DynaGraft sometimes may only induce calcification, and not bone formation.

Figure 12
Osteotech, Inc.
Osteoinductivity Dose Response



Source: *Journal of Periodontology*; William Blair & Company, L.L.C.

Growth Opportunities

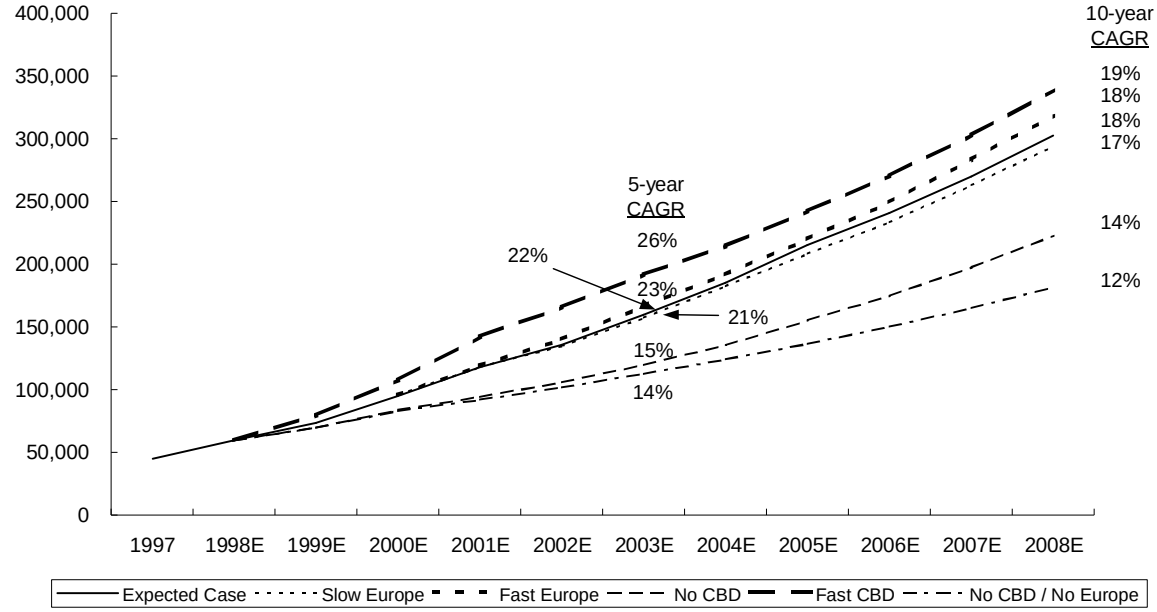
We believe that three levers will drive Osteotech's earnings growth: 1) revenue growth and margin expansion of the core U.S. business, predominantly though the increase of Grafton® DBM sales, from about $22 million in 1997 to $51 million in 2000; 2) introduction of allograft threaded cortical bone dowels by Osteotech into the U.S. interbody fusion cage market in 1999, which should add as much as $12 million in incremental revenue by 2000; and 3) expansion of the allograft business—both Grafton® DBM and base allograft parts—into Europe by 2000, facilitated by the recent OST investment. In addition, Osteotech shares could have potential EPS upside due to its U.S. distribution agreement with Ulrich for metal spine systems and its hydroxyapatite technology in Europe.

Table 7 details our estimates of the company's revenue by product line, as well as our short-term forecasts. In addition, we have conducted a sensitivity analysis of Osteotech's total revenue to success of the two new initiatives—threaded cortical bone dowels and the European expansion of its core allograft business; this sensitivity analysis is depicted in figure 13, on the next page. The base compounded annual growth rate (CAGR) is 22% for five years. From this analysis, we can observe that the revenue growth is most sensitive to the rate of success of the threaded cortical bone dowels, with the five-year CAGR varying between 15% and 26%, depending on threaded cortical bone dowel sales. The forecast is less sensitive to European success, with the five-year CAGR varying between 21% and 23%. One of the most important results of the sensitivity analysis is that if the U.S. core business remains healthy, but there is absolutely no success in the CBD or European initiatives, Osteotech still would have a 14% five-year CAGR in revenue. As discussed in our valuation section, we believe that most of the potential upside from the CBD and European growth initiatives has not yet been fully included in the stock price, making its current price attractive given our expectation that the revenue growth rate will be 22%, versus 14%.

Table 7
Osteotech, Inc.
Product Line Estimates
($ in thousands)

	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998E	1999E	2000E
U.S. Grafton					$1,756	$4,578	$5,494	$7,527	$12,570	$21,871	**$33,703**	**$41,953**	**$51,009**
U.S. Base Allograft	$208	$2,026	$7,127	$9,295	10,436	11,717	15,530	16,026	18,389	19,302	**21,411**	**22,925**	**26,025**
CBD												**3,500**	**11,000**
U.S. Ulrich						72	133	210	248	280	**300**	**360**	**450**
U.S. Misc. Products			404	391	709	677	781	530	375	434	**450**	**500**	**575**
European Grafton													**351**
European Base Allograft													**405**
Europe Service (coatings)					615	738	1,052	898	758	1,688	**3,101**	**3,566**	**3,923**
Europe Product (ceramics)					800	1,065	1,061	1,942	1,858	1,086	**652**	**500**	**750**
Grant					335	277	519	801	697	13			
License fees										257	**124**	**125**	
ConvaTec													**333**
Total	208	2,026	7,531	9,686	14,651	19,124	24,570	27,934	34,895	44,931	**59,740**	**73,429**	**94,821**
Year-over-year Growth		874%	272%	29%	51%	31%	28%	14%	25%	29%	**33%**	**23%**	**29%**

Figure 13
Osteotech, Inc.
Revenue Sensitivity Analysis
($ in thousands)



Source: Osteotech, Inc. and competitor financials; industry interviews; MTF; ARC; UFTB; MDI; MarketLine; Frost & Sullivan; Dun & Bradstreet; Theta; William Blair & Company, L.L.C. estimates

Continued Growth and Margin Expansion of U.S. Core Business

The U.S. market for allografts and bone graft material should continue to grow rapidly. We estimate that the U.S. market for base allografts, proprietary bone graft materials such as Grafton® DBM, and other synthetic bone graft materials will be approximately $216 million at the end-user level in 1998. Furthermore, as shown in figure 3, we believe that this market will grow at a compounded annual rate of 14% through 2003, leading to a market size of about $420 million.

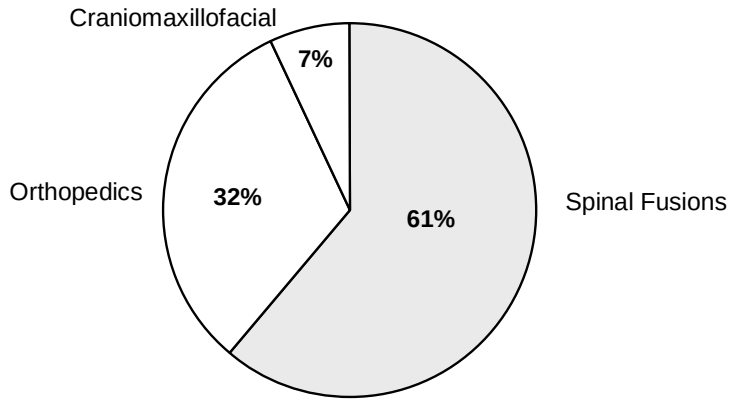
There is considerable room in the market for Osteotech to penetrate. Figure 14 shows the end-use sales of Grafton® DBM by site of procedure. When we compare this with the overall procedure volume by site, we find that (as shown in figure 15) 89% of the market remains unpenetrated. Specifically, Grafton® DBM is used in only 14% of spine fusions, 10% of general orthopedic procedures, and 4% of maxillofacial procedures.

Margins also should continue to improve significantly. We expect significant, continued reductions in COS, SG&A, and R&D as a percentage of revenue. While the reduction in COS partly is driven by volume, it mainly is driven by a mix shift to the higher gross margin, proprietary products such as Grafton® DBM, and the reduction in sales of the current low-gross-margin European products. Grafton® DBM products should make up 57% of revenue in 1998, compared with 49% in 1997 and 37% in 1996. Also, we forecast that the high-gross-margin products (Grafton® DBM and CBDs) should make up 63% and 67% of revenue in 1999 and 2000, respectively. Consequently, 1997 gross margin of 65% should increase to 71% by 2000. SG&A also should continue to decline in the future, due to leveraging of Osteotech's fixed sales and marketing and overhead costs, and the effects of the mix shift mentioned above. We anticipate slightly more than a 100-basis-point reduction in SG&A in 1999 and about a 50-basis-point reduction in 2000. The reason for the acceleration in 1999 also is due mostly to the mix shift, with some contribution from leveraging

overhead. R&D expenses have declined in recent years, since the company halted its PolyActive™ polymer program in 1996. We foresee small nominal increases from this new base going forward, but a decline as a percentage of revenue, from 8% in 1997 to 5% in 2000.

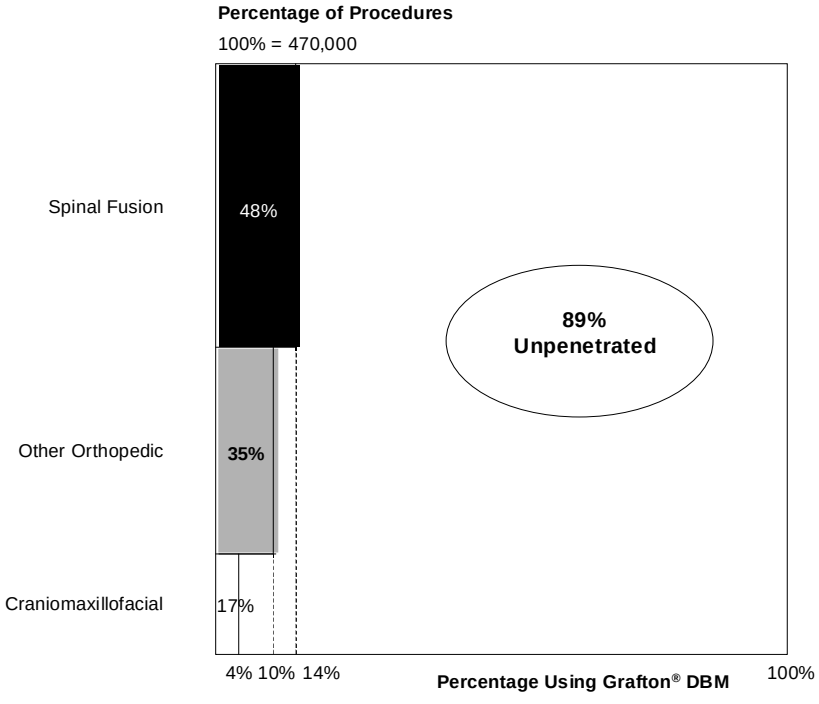
Figure 14
Osteotech, Inc.
End-uses of Grafton

1997
100% = 51,000 Procedures



Source: Osteotech, Inc.; William Blair & Company, L.L.C. estimates

Figure 15
Osteotech, Inc.
Grafton® DBM Penetration

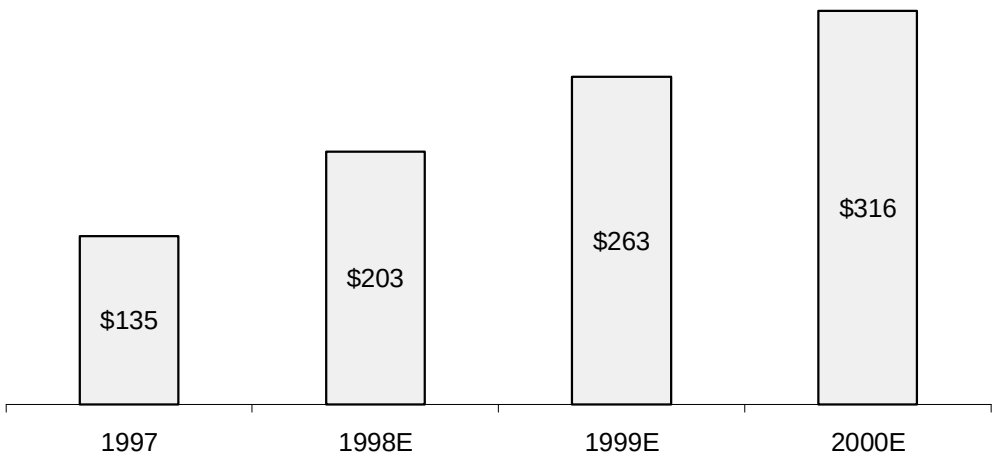


Source: Osteotech, Inc.; William Blair & Company, L.L.C. analysis

Introduction of Threaded Cortical Bone Dowels

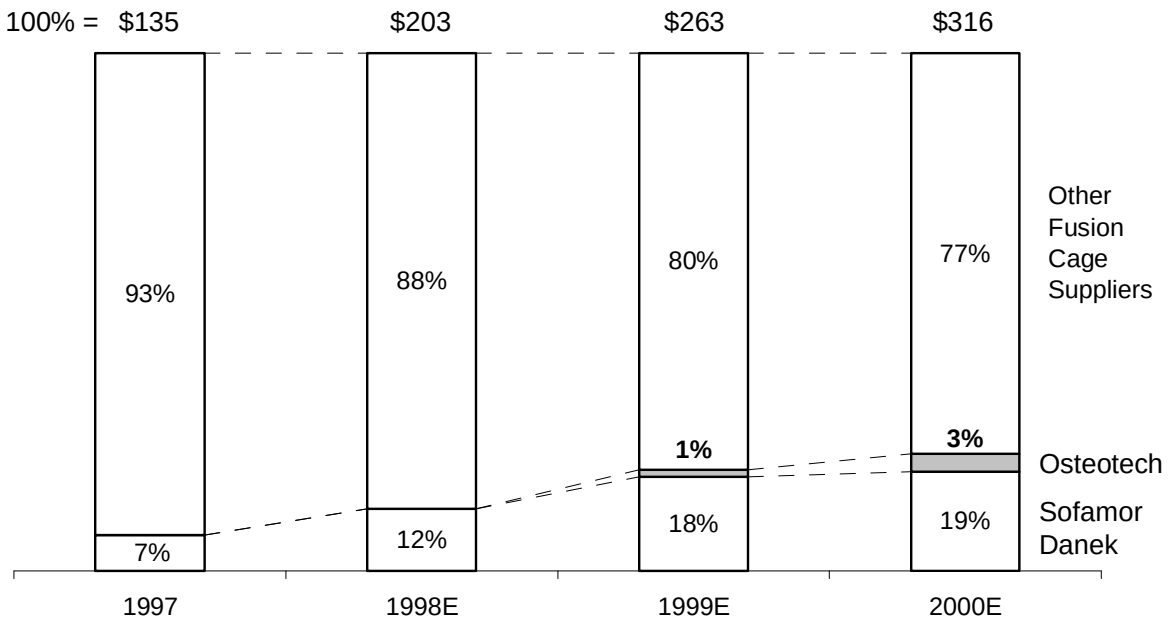
Threaded cortical bone dowels provide an exceptional growth opportunity. Threaded cortical bone dowels (CBD) are targeted at one of the fastest-growing medical device segments—interbody fusion cages. As shown in figure 16, we estimate that the U.S. market for interbody fusion cages will grow from $135 million in 1997 to $316 million by 2000. In this market, Sofamor Danek Group, along with the University of Florida Tissue Bank, pioneered the marketing of threaded CBDs, its MD product line, as a substitute for metal interbody fusion cages, such as Sulzer Medica Spine-Tech's BAK cage, or Spinal Dynamics' Ray cage. However, Sofamor Danek has been supply-constrained in its ability to sell more CBDs. Osteotech, with its superior allograft-supply position, the market position with spinal surgeons afforded it by its Grafton® DBM franchise, and its 220-person-strong salesforce, should be able to capture at least a modest share of this market. We estimate sales of $5 million in 1999 and $12 million in 2000 for the Osteotech CBDs, compared with an overall U.S. cage market of $263 million and $316 million in 1999 and 2000, respectively. As shown in figure 17, this would mean that the company would have a modest 2% share in 1999 and a 4% share in 2000, with CBDs having overall shares, or 20% and 23%, respectively.

Figure 16
Osteotech, Inc.
U.S. Fusion Cage Market Size
($ in millions)



Source: Osteotech, Inc. and competitor financials; U.S. Census Bureau; MDI; MarketLine; Theta; Frost & Sullivan; Dun & Bradstreet; industry interviews; NCHS; William Blair & Company, L.L.C. estimates

Figure 17
Osteotech, Inc.
CBD Share of Fusion Cage Market
($ in millions)



Source: Osteotech, Inc. and competitor financials; U.S. Census Bureau; MDI; MarketLine; Theta; Frost & Sullivan; Dun & Bradstreet; industry interviews; NCHS; William Blair & Company, L.L.C. estimates

Expansion to Europe

The potential for allograft bone and bone graft material in Europe is comparable to the total U.S. market size. However, the European allograft bone and bone graft material market still is highly fragmented, with much of the material supplied by local, not-for-profit, hospital-based tissue banks. This should provide Osteotech with an excellent opportunity to expand internationally to Europe, leveraging its proven business model and core bone processing skills.

Europe is not a single market for bone grafts. Surgical practices vary among the different countries, as do cultural issues. In addition, bone tissue donation is not widespread, and the percentage of the population donating bone tissue typically is lower than in the United States. This should provide a good opportunity for Osteotech and its clients, such as the MTF, to provide proven skills and techniques to increase donation.

However, there also are similarities among the European markets, compared to the United States. In Europe, there is a great deal of concern regarding safety and the reduction of potential for infectious-disease transmission. European regulations and attitudes, even more so than those in the United States, favor processes that have validated proof of viral inactivation. Also, most European surgeons make decisions on the basis of solid clinical research, and much research on Grafton® DBM exists.

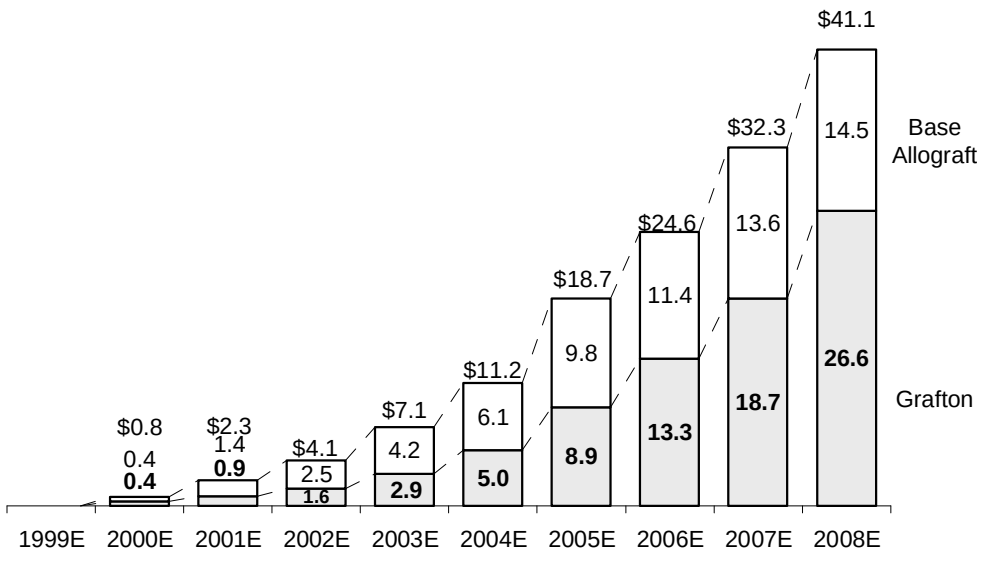
The two largest potential markets for Osteotech are Germany and France. However, Grafton® DBM likely will be considered as a form of drug in Germany, whereas tissue regulations are less cumbersome in France. Hence, the company's first targeted European country will be France. That said, drug regulations in Germany, as in the rest of Europe, are not as onerous as in the United States and more like U.S. device regulations, and we expect a German launch by 2001.

Acquisition of majority interest in OST. To take advantage of this opportunity, Osteotech agreed that it would acquire a majority stake in OST Developpement SA (OST), a subsidiary of Transphyto SA, Clermont-Ferrand, France, on June 25, 1998. The aggregate cost of acquiring its 90% stake should be approximately $1.5 million. OST's initial products were bovine grafts—named LUBBOC and LADDEC—for human orthopedic and dental uses; OST received a CE mark (the European equivalent of FDA approval) for the grafts and the validated viral inactivation process that produced them. Recently, OST has developed a system to process human tissue as well, and has signed a long-term agreement with a French tissue bank, Osteo Banque D'Auvergne (OBA), to process and distribute femur heads recovered from live donors during hip replacement surgery.

Osteotech is applying for tissue bank status in France so that it may provide allow allograft tissue services, including donor recovery. In the meantime, it may import Grafton® DBM from the United States through OBA and process certain bone tissues locally through OST, such as femural heads mentioned above. Initially, all of the donor tissue to be supplied as Grafton® DBM will be processed in the United States, as it will take 2 to 3 years to establish a donor recovery program.

As figure 18 illustrates, we believe that this initiative should add slightly less than $800,000 in incremental allograft and Grafton® DBM sales in 2000, with revenue approximately doubling, on average, every subsequent year in the short term, leading to sales of almost $19 million in 2005.

Figure 18
Osteotech, Inc.
Incremental European Allograft Sales
($ in millions)



Source: William Blair & Company, L.L.C. estimates

Other Upside Potential

Since 1993, Osteotech has distributed metal, spinal implants in the United States for the German firm Heinrich C. Ulrich. The first implant the company distributed was the VDS Zielke system for anterior correction of spinal deformities, as well as Ulrich's line of more than 250 high-quality, specialty surgical instruments. Recently, the company has begun to market Ulrich's SSCS posterior thoracolumbar low-profile, hinged load-sharing system. Osteotech receives a distributor margin from Ulrich based on sales, which we believe is greater than the typical 30% received by a stocking orthopedic distributor. However, the greatest benefit of having these devices as part of the company's overall product line is the incremental leverage it provides Grafton® DBM sales, not the distributor profit Osteotech receives. By having these products in their product portfolio, Osteotech's sales agents have greater access to the spine surgeons that control the largest segment of the bone graft market.

Osteotech has two other areas in which it has potential revenue upside—its CAM Implant hydroxyapatite technology and its U.S. distribution of Ulrich's metal spinal implants. For example, through its CAM Implants subsidiary, the company has established a long-term arrangement to be the exclusive supplier of medical-grade, hydroxyapatite (HA) granules to ConvaTec, a division of Bristol-Myers Squibb. These granules are a key component for the urethral sphincter augmentation device made by ConvaTec. Currently, ConvaTec is conducting the necessary clinical trials in the United States and Europe and believes that it will begin marketing the device sometime in late 1999 or early 2000 in Europe and likely later in the U.S. Osteotech's sales to ConvaTec should exceed $3 million by 2005. In addition to providing the HA raw material, CAM Implants provides HA plasma spray and technology, as well as titanium plasma spray technology through its alliance with APS, a metal-coating firm. The company's largest customer for HA plasma coating technology is Osteonics, a subsidiary of Stryker. In addition to providing CAM Implant with the titanium plasma spray technology in Europe, its alliance with APS provides it with a U.S. distribution partner that will sell CAM Implants HA raw material and provide royalties on licenses of its technology.

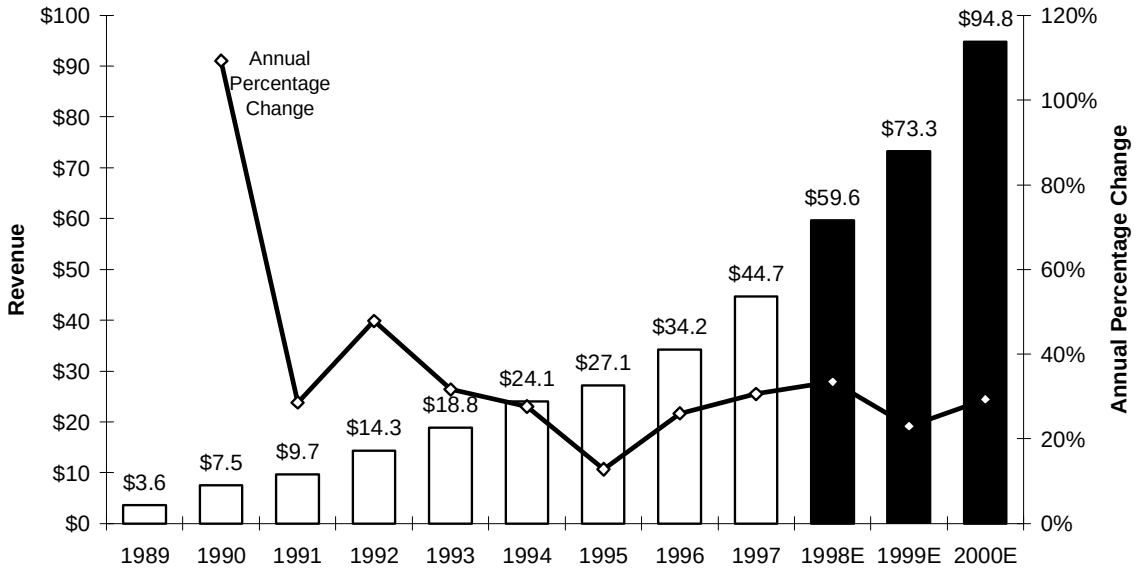
Financials

Operating Results and Forecast

Tables 8 and 9 contain our annual income statement and quarterly model, respectively. We give a more-detailed discussion of our expected results, as well as the drivers of those results, below.

Revenue. We believe that Osteotech's revenue and profit growth should continue to be strong, driven by its core U.S. business, as well as new business in Europe and sales of threaded cortical bone dowels (CBD). As shown in figure 19, revenue growth has been greater than 25%, on average, over the past five years, with a compounded annual growth rate of more than 27%. We expect this pace to continue, with expected revenue growth rates of 33% for 1998, and between 25%-30% for 1999 and 2000. Through 2003, we forecast a compounded annual revenue growth of 22%. As mentioned, the growth rate is sensitive to continued success in the company's core business, as well as CBD sales and European penetration. Consequently, if all of these achieve higher-than-expected success, the 5-year compounded annual growth rate could be 26%, but even if the new product initiatives have no success at all, the revenue growth rate still should be a robust 14% (see sensitivity analysis shown in figure 13).

Figure 19
Osteotech, Inc.
Revenue and Growth Rate*
($ in millions)



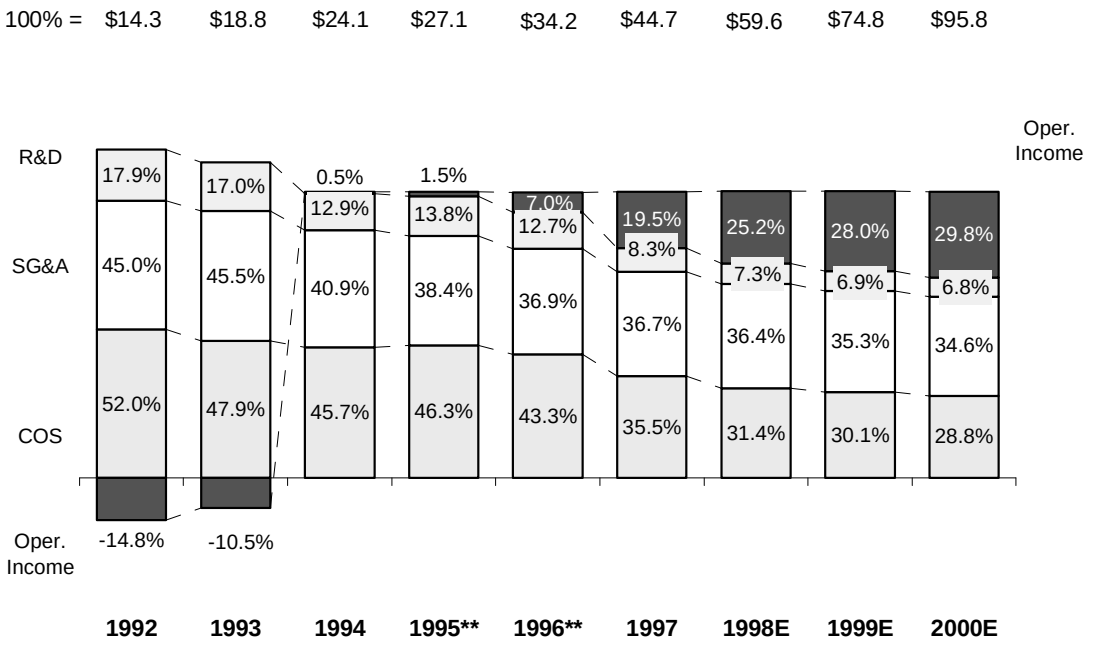
* Excludes grants and licensing fees

Source: Company financials; William Blair & Company, L.L.C. estimates

Our product-line revenue estimates and forecast also are shown in table 7; they are discussed more extensively in the "Growth Opportunity" section of this report.

Gross margin. As mentioned in the "Investment Recommendation" section and shown in figure 20, we expect significant continued reductions as a percentage of revenue in COS, SG&A, and R&D. While the reduction in COS partly is driven by volume, it mainly is driven by a mix shift to the higher-gross-margin Grafton® DBM products, as well as CBD products, and the reduction in sales of the current low-gross-margin European products. As shown in figure 21, Grafton® DBM products should make up 57% of revenue in 1998, compared with 49% in 1997 and 37% in 1996. Even as the revenue from CBDs begins to become a larger portion of the mix, the percentage generated from Grafton® DBM products should be relatively stable over the next few years, at 56% in 1999 and 54% in 2000. We forecast that the high-margin CBD sales will account for 5% of revenue in 1999 and 12% in 2000. All of this means that the lower-margin base allograft sales should account for a smaller percentage of revenue every year, declining from 43% in 1997 to only 28% in 2000. Grafton® DBM has about a 2 times greater gross margin than base allograft. Volume has a lower effect in reducing COS, because the processing of allograft products is not readily automated, as each donor must be preserved as a single production lot, with many steps taken to ensure no commingling of donors during the processing and disinfection of processing equipment between donors. However, there are some efficiencies still possible to achieve in the labor-driven process as volumes increase. Overall, we believe that Osteotech's gross margin of more than 65% is very good for a medical-device business, and should increase to 71% by 2000.

Figure 20
Osteotech, Inc.
COS and Operating Expenses*
($ in millions)

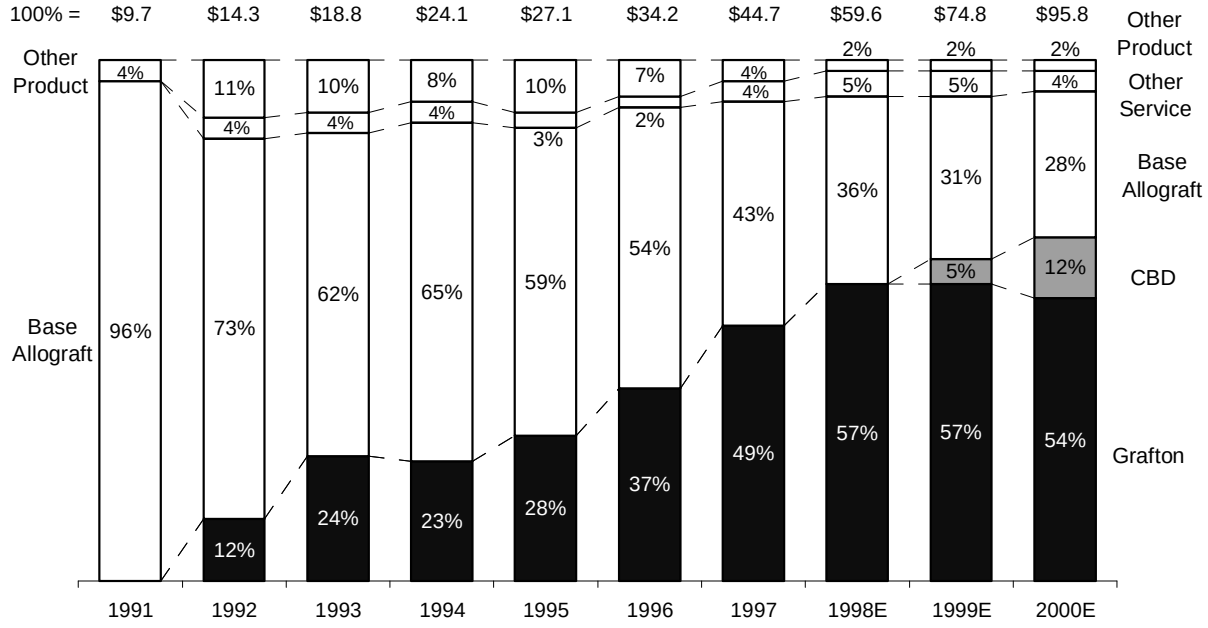


* Excludes grants and licensing fees

** Adjusted for one-time charges (1995 termination of distribution agreement; 1996 restructuring)

Source: Company financials; William Blair & Company, L.L.C. estimates

Figure 21
Osteotech, Inc.
Revenue Mix*
($ in millions)



* Excludes grants and licensing fees

Source: Company financials; competitor financials; interviews; William Blair & Company, L.L.C. estimates

Operating margin. SG&A expense ratio also should continue to decline in the future, due to the leveraging of the company's fixed sales and marketing and overhead costs, and the effects of the mix shift mentioned above. We anticipate a reduction in SG&A by slightly more than 1% 1999 and 0.5% in 2000; the accelerated reduction in 1999 is due mostly to the mix shift. The independent agents that sell for Osteotech are paid a flat fee based on the end-user price (about 10%), but as revenue increases the internal fixed costs to support the agents can be spread across the total revenue. The net result will be an SG&A expense of 34.6% in 2000 versus 36.5% in 1997.

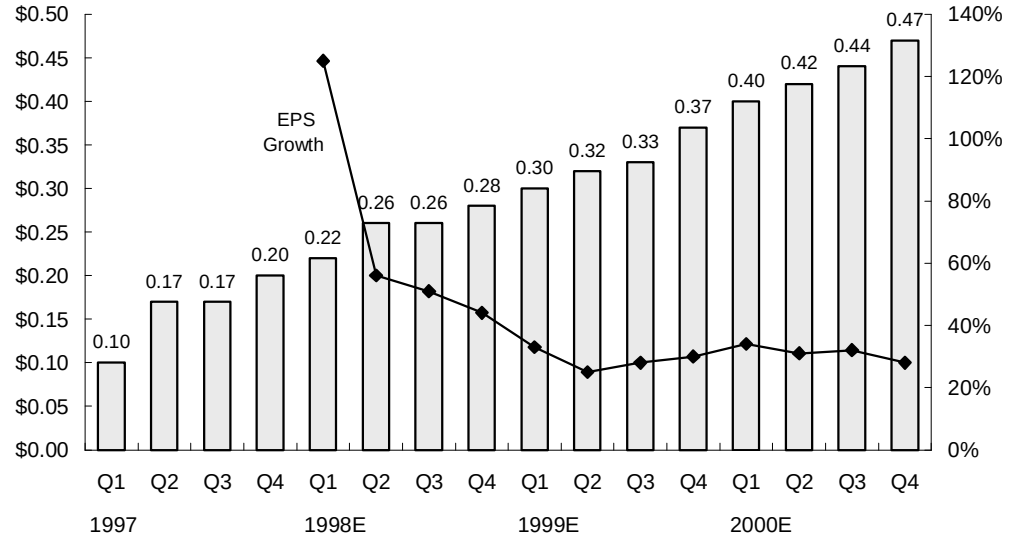
R&D expenses have declined in recent years since the company halted its PolyActive™ polymer program in 1996. This should stabilize as a percent of sales, as Osteotech continues to provide R&D support to current products, as well as developing new proprietary allograft products and manufacturing processes.

Other expenses and taxes. Due to debt that will be taken on in 1999 to construct a new production facility, interest expenses are estimated to be almost $500 thousand in 1999 and $1.5 million in 2000, equating to a cost of $0.05 and $14 per share respectively. We view this as an important investment to secure sufficient capacity as the amount of donor tissue processed grows, and as Osteotech adds new, proprietary and high-margin products such as the threaded cortical bone dowels.

The effective income tax rate, which has varied significantly over the past few years, should remain relatively constant, at about 41%.

Net income and EPS. As shown in table 9 and figure 22, quarterly net income and EPS should continue to increase through 2000. We estimate that net income growth will vary between 28 to 48%, and EPS growth should be between 25 to 50% until 2000. During this period, we estimate that the number of diluted shares outstanding will increase annually by about 6%, accounting for an EPS growth rate lower than the net income growth rate. In the period 1999 to 2000, we believe that quarterly EPS growth rates should peak in the first quarter of 2000 at 34%, and decline to 29% by fourth quarter 2000, as detailed in table 9. We forecast annual EPS growth of 58% in 1998, 29% in 1999, and 32% in 2000, as shown in table 8.

Figure 22
Osteotech, Inc.
EPS and EPS Growth



Source: William Blair & Company, L.L.C. estimates

Balance Sheet and Cash Flow

Two important points should be noted regarding Osteotech's balance sheet and cash position. First, the long-term debt load, which is currently approximately zero, will increase to 23% of total assets in 1999 due to construction of a new production facility. This debt load should decline relatively quickly to 16% by the end of 2000. Second, as shown tables 10 and 11, Osteotech has a significant cash and short-term investment balance for a business its size, with $20 million forecast for the end of 1998, and we expect this balance to triple to more than $60 million by the end of 2000. This increase is made possible by cash generated from operating activities, which we estimate at $12 million in 1998, $18 million in 1999 and $25 million in 2000, thus making its growth self-funding, as well as providing the resources to make the necessary investments, such as the one made with OST.

Valuation

We believe that Osteotech shares currently are undervalued. As shown in figure 23, on page 36, Osteotech currently appears valued more similarly to small-cap orthopedic competitors such as Interpore Cross and Exactech instead of its large-cap orthopedic brethren like Biomet and Stryker when comparing estimated 1999 P/E ratios with forecast 1997-1999 EPS growth rates. Also, as shown in figure 23, the small-cap competitors appear to show no correlation with growth, in contrast to the large-cap names. Thus, using current stock prices, Osteotech has a 1999 P/E ratio of 22 times, versus a 42% EPS growth rate, similar to the average small-cap P/E ratio of 19. However, as figure 24, on page 36, illustrates, the company's market capitalization actually is well between the two orthopedic groups. This data, combined with the company's strong franchise and profitability and growth potential, leads us to believe that Osteotech is less risky than the firms with which it is implicitly valued. Consequently, we believe it should be valued between the two orthopedic groups. Additionally, it appears that its 1999 P/E ratio does not fully incorporate the probable upside potential of its CBD and international growth initiatives. In conclusion, we would estimate that a more appropriate P/E ratio would be 25-30 times forecast 1999 per-share earnings on the basis of our intermediate-term EPS growth rate of more than 30%.

Additional information in available upon request.

DJIA:	8028.77
S&P 500:	1044.75
NASDAQ:	1743.59

William Blair & Company, L.L.C. maintains a market in the shares of Osteotech, Inc.

The prices of the common stock of other public companies mentioned in this report follow:

Arthrocare	$13 1/8	Johnson & Johnson	$77 13/16
Biomet	$34	Orthofix	$11 5/16
Bristol-Myers Squibb	$100 5/8	Orthologic	$3 23/32
Cohesion Technologies	$3 1/2	Pfizer	$106 11/16
Creative Biomolecules	$2 13/16	Sofamor Danek	$89 5/16
DePuy	$35 5/8	Stryker	$35 3/16
Encore Medical	$2 11/16	Sulzer Medica	$17 7/8
Exactech	$6 5/8	United States Surgical	$42 3/8
Interpore Cross	$3 13/16		

Table 8
Osteotech, Inc.
Annual Income Statement Model
($ in thousands)

	1997	Year-over-year Growth	1998E	Year-over-year Growth	1999E	Year-over-year Growth	2000E	Year-over-year Growth
Service Fee	$ 42,861	35.1%	**$ 58,215**	**35.8%**	**$ 71,944**	**23.6%**	**$ 92,713**	**28.9%**
Product Sales	1,800	-27.4%	**1,402**	**-22.1%**	**1,360**	**-3.0%**	**2,108**	**55.0%**
License Fees	257		**124**		**125**		**0**	
Grants	13		**0**		**0**		**0**	
Net Revenues	44,931	28.8%	**59,740**	**33.0%**	**73,429**	**22.9%**	**94,821**	**29.1%**
Cost of Services	14,487	16.8%	**17,713**	**22.3%**	**21,048**	**18.8%**	**25,761**	**22.4%**
Cost of Products	1,348	-44.2%	**983**	**-27.1%**	**985**	**0.2%**	**1,503**	**52.7%**
Total Cost of Sales	15,835	6.8%	**18,695**	**18.1%**	**22,033**	**17.9%**	**27,264**	**23.7%**
Gross Margin	29,096	44.9%	**41,045**	**41.1%**	**51,396**	**25.2%**	**67,557**	**31.4%**
SG&A	16,381	29.8%	**21,701**	**32.5%**	**25,872**	**19.2%**	**32,801**	**26.8%**
R&D	3,728	-14.4%	**4,332**	**16.2%**	**5,036**	**16.2%**	**6,490**	**28.9%**
Total Operating Expenses	20,109	9.7%	**26,033**	**29.5%**	**30,908**	**18.7%**	**39,291**	**27.1%**
Operating Income	8,987	413.8%	**15,012**	**67.0%**	**20,488**	**36.5%**	**28,266**	**38.0%**
Interest Income	673	50.2%	**1,032**	**53.3%**	**1,523**	**47.6%**	**3,208**	**110.6%**
Interest Expense	(140)	-39.7%	**(77)**	**-44.9%**	**(526)**	**581.4%**	**(1,467)**	**179.1%**
Other	52	-5.5%	**247**	**375.1%**	**279**	**13.0%**	**366**	**31.0%**
Non-operating Income (Expense)	585	115.9%	**1,202**	**105.5%**	**1,277**	**6.2%**	**2,107**	**65.0%**
Earnings Before Income taxes	9,572	373.9%	**16,214**	**69.4%**	**21,765**	**34.2%**	**30,373**	**39.6%**
Income Tax Provision	3,886	65.8%	**6,642**	**70.9%**	**8,924**	**34.4%**	**12,454**	**39.6%**
Net Income (Loss)	5,686	NM	**9,571**	**68.3%**	**12,841**	**34.2%**	**17,919**	**39.6%**
Weighted Average Shares Outstanding	8,793	11.0%	**9,360**	**6.5%**	**9,746**	**4.1%**	**10,346**	**6.2%**
EPS	0.65	NM	**1.02**	**58.1%**	**1.32**	**28.9%**	**1.73**	**31.5%**
100% Income Statement								
	1997		**1998E**		**1999E**		**2000E**	
Service Fee	95.4%		**97.4%**		**98.0%**		**97.8%**	
Product Sales	4.0%		**2.3%**		**1.9%**		**2.2%**	
License Fee	0.6%		**0.2%**		**0.2%**		**0.0%**	
Grants	0.0%		**0.0%**		**0.0%**		**0.0%**	
Net Revenues	100.0%		**100.0%**		**100.0%**		**100.0%**	
Cost of Services (Percentage of Service Fee)	33.8%		**30.4%**		**29.3%**		**27.8%**	
Cost of Products (Percentage of Product Revenue)	74.9%		**70.1%**		**72.4%**		**71.3%**	
Total Cost of Sales (Excludes Grants & License Fees)	35.5%		**31.4%**		**30.1%**		**28.8%**	
Gross Margin (Excludes Grants & License Fees)	65.1%		**68.8%**		**70.1%**		**71.2%**	
SG&A	36.5%		**36.3%**		**35.2%**		**34.6%**	
R&D	8.3%		**7.3%**		**6.9%**		**6.8%**	
Total Operating Expenses	44.8%		**43.6%**		**42.1%**		**41.4%**	
Operating Income	20.0%		**25.1%**		**27.9%**		**29.8%**	
Interest Income	1.5%		**1.7%**		**2.1%**		**3.4%**	
Interest Expense	-0.3%		**-0.1%**		**-0.7%**		**-1.5%**	
Other	0.1%		**0.4%**		**0.4%**		**0.4%**	
Non-Operating Income (Expense)	1.3%		**2.0%**		**1.7%**		**2.2%**	
Earnings Before Income taxes	21.3%		**27.1%**		**29.6%**		**32.0%**	
Income Tax Provision (% of EBIT)	40.6%		**41.0%**		**41.0%**		**41.0%**	
Net Income (Loss)	12.7%		**16.0%**		**17.5%**		**18.9%**	

Table 9
Osteotech, Inc.
Quarterly Income Statement Model
($ in thousands)

	1997				1998E				1999E				2000E			
	1st	2nd	3rd	4th	1st (A)	2nd (A)	3rd	4th	1st	2nd	3rd	4th	1st	2nd	3rd	4th
Service Fee	$ 9,478	$ 9,887	$ 11,551	$11,945	$13,157	$ 14,927	$ 14,461	$ 15,670	$ 16,447	$ 17,232	$ 18,216	$ 20,048	$ 21,602	$ 22,529	$ 23,456	$ 25,125
Product Sales	606	559	382	253	318	203	441	439	370	345	324	322	489	536	502	584
License Fees		257				124				125						
Grants				13												
Net Revenues	10,084	10,703	11,933	12,211	13,475	15,254	14,902	16,109	16,817	17,702	18,540	20,371	22,091	23,065	23,958	25,709
Cost of Services	3,420	3,526	3,971	3,570	4,053	4,461	4,462	4,737	4,913	5,091	5,314	5,730	6,083	6,293	6,503	6,882
Cost of Products	452	410	246	240	174	178	316	315	267	250	235	234	349	381	358	415
Total Cost of Sales	3,872	3,936	4,217	3,810	4,227	4,639	4,778	5,051	5,180	5,341	5,549	5,964	6,432	6,674	6,861	7,297
Gross Margin	6,212	6,767	7,716	8,401	9,248	10,615	10,124	11,058	11,638	12,362	12,991	14,407	15,659	16,391	17,097	18,412
S,G&A	3,798	3,831	4,317	4,435	4,819	5,762	5,366	5,754	5,982	6,227	6,537	7,126	7,680	7,994	8,282	8,845
R&D	936	890	861	1,041	1,129	1,077	1,033	1,093	1,199	1,173	1,299	1,365	1,545	1,512	1,674	1,759
Total Operating Expenses	4,734	4,721	5,178	5,476	5,948	6,839	6,399	6,847	7,181	7,400	7,836	8,491	9,225	9,506	9,956	10,604
Operating Income	1,478	2,046	2,538	2,925	3,300	3,776	3,725	4,211	4,457	4,961	5,155	5,916	6,435	6,885	7,141	7,808
Interest Income	131	138	189	215	240	271	264	257	286	325	394	519	684	783	823	918
Interest Expense	(48)	(31)	(30)	(31)	(28)	(22)	(13)	(14)	(24)	(66)	(145)	(291)	(383)	(373)	(359)	(352)
Other	9	35	15	(7)	40	100	51	56	62	67	72	78	83	89	94	100
Non-operating Income (Expense)	92	142	174	177	252	349	302	299	323	327	321	306	385	499	557	665
Earnings Before Income Taxes	1,570	2,188	2,712	3,102	3,552	4,125	4,028	4,509	4,780	5,288	5,476	6,222	6,820	7,383	7,698	8,474
Income Tax Provision	738	785	1,104	1,259	1,446	1,696	1,651	1,849	1,960	2,168	2,245	2,551	2,796	3,027	3,156	3,474
Net Income (Loss)	832	1,403	1,608	1,843	2,106	2,429	2,376	2,661	2,820	3,120	3,231	3,671	4,024	4,356	4,542	4,999
Year-over-year Growth	387%	595%	541%	-294%	153%	73%	48%	44%	34%	28%	36%	38%	43%	40%	41%	36%
Weighted Average Shares Outstanding (000)	8,374	8,479	9,419	9,355	9,439	9,391	9,241	9,371	9,521	9,671	9,821	9,971	10,121	10,271	10,421	10,571
EPS	0.10	0.17	0.17	0.20	0.22	0.26	0.26	0.28	0.30	0.32	0.33	0.37	0.40	0.42	0.44	0.47
Year-over-year Growth					125%	56%	51%	44%	33%	25%	28%	30%	34%	31%	32%	28%
100% Income Statement																
Service Fee	94.0%	92.4%	96.8%	97.8%	97.6%	97.9%	97.0%	97.3%	97.8%	97.3%	98.3%	98.4%	97.8%	97.7%	97.9%	97.7%
Product Sales	6.0%	5.2%	3.2%	2.1%	2.4%	1.3%	3.0%	2.7%	2.2%	2.0%	1.7%	1.6%	2.2%	2.3%	2.1%	2.3%
License Fee	0.0%	2.4%	0.0%	0.0%	0.0%	0.8%	0.0%	0.0%	0.0%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Grants	0.0%	0.0%	0.0%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Net Revenues	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Cost of Services (Percentage of Service Fee)	36.1%	35.7%	34.4%	29.9%	30.8%	29.9%	30.9%	30.2%	29.9%	29.5%	29.2%	28.6%	28.2%	27.9%	27.7%	27.4%
Cost of Products (Percentage of Product Revenue)	74.6%	73.3%	64.4%	94.9%	54.7%	87.7%	71.6%	71.6%	72.1%	72.3%	72.5%	72.5%	71.4%	71.2%	71.3%	71.1%
Total Cost of Sales (Excludes Grants & License Fees)	38.4%	37.7%	35.3%	31.2%	31.4%	30.7%	32.1%	31.4%	30.8%	30.4%	29.9%	29.3%	29.1%	28.9%	28.6%	28.4%
Gross Margin (Excludes Grants & License Fees)	61.6%	64.8%	64.7%	68.9%	68.6%	70.2%	67.9%	68.6%	69.2%	70.3%	70.1%	70.7%	70.9%	71.1%	71.4%	71.6%
SG&A	37.7%	35.8%	36.2%	36.3%	35.8%	37.8%	36.0%	35.7%	35.6%	35.2%	35.3%	35.0%	34.8%	34.7%	34.6%	34.4%
R&D	9.3%	8.3%	7.2%	8.5%	8.4%	7.1%	6.9%	6.8%	7.1%	6.6%	7.0%	6.7%	7.0%	6.6%	7.0%	6.8%
Total Operating Expenses	46.9%	44.1%	43.4%	44.8%	44.1%	44.8%	42.9%	42.5%	42.7%	41.8%	42.3%	41.7%	41.8%	41.2%	41.6%	41.2%
Operating Income	14.7%	19.1%	21.3%	24.0%	24.5%	24.8%	25.0%	26.1%	26.5%	28.0%	27.8%	29.0%	29.1%	29.8%	29.8%	30.4%
Interest Income	1.3%	1.3%	1.6%	1.8%	1.8%	1.8%	1.8%	1.6%	1.7%	1.8%	2.1%	2.5%	3.1%	3.4%	3.4%	3.6%
Interest Expense	-0.5%	-0.3%	-0.3%	-0.3%	-0.2%	-0.1%	-0.1%	-0.1%	-0.1%	-0.4%	-0.8%	-1.4%	-1.7%	-1.6%	-1.5%	-1.4%
Other	0.1%	0.3%	0.1%	-0.1%	0.3%	0.7%	0.3%	0.3%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%
Non-Operating Income (Expense)	0.9%	1.3%	1.5%	1.4%	1.9%	2.3%	2.0%	1.9%	1.9%	1.8%	1.7%	1.5%	1.7%	2.2%	2.3%	2.6%
Earnings Before Income Taxes	15.6%	20.4%	22.7%	25.4%	26.4%	27.0%	27.0%	28.0%	28.4%	29.9%	29.5%	30.5%	30.9%	32.0%	32.1%	33.0%
Income Tax Provision (% of EBIT)	47.0%	35.9%	40.7%	40.6%	40.7%	41.1%	41.0%	41.0%	41.0%	41.0%	41.0%	41.0%	41.0%	41.0%	41.0%	41.0%
Net Income (Loss)	8.3%	13.1%	13.5%	15.1%	15.6%	15.9%	15.9%	16.5%	16.8%	17.6%	17.4%	18.0%	18.2%	18.9%	19.0%	19.4%

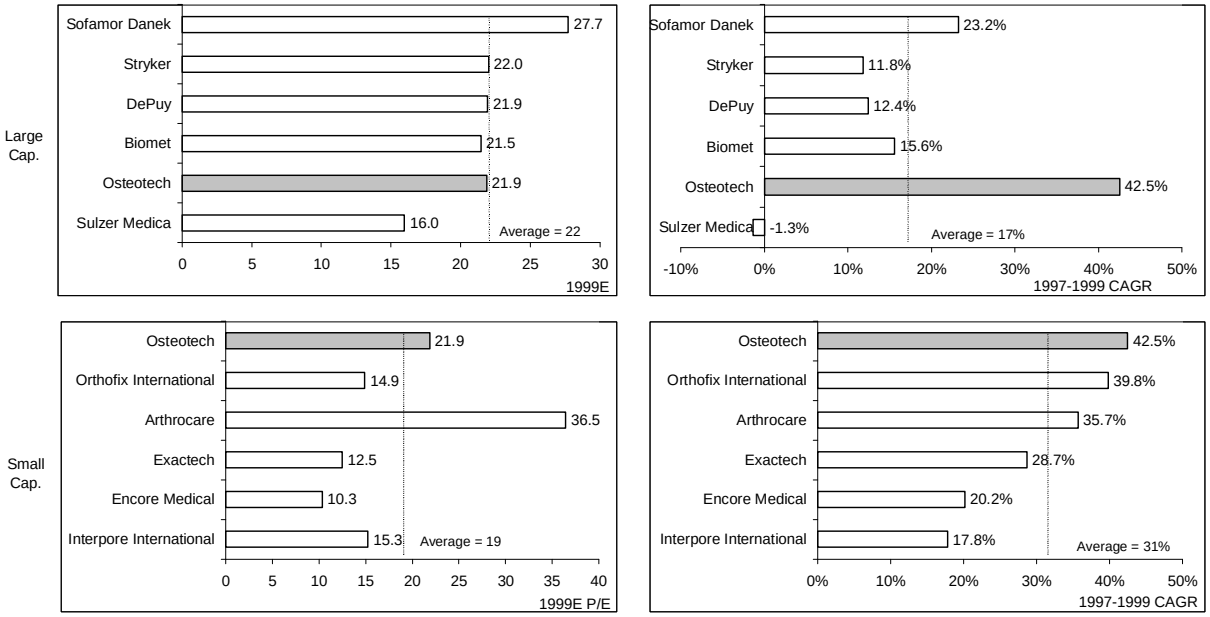
Table 10
Osteotech, Inc.
Annual Balance Sheet Model
($ in thousands)

	1997	1998E	1999E	2000E
Assets				
Current Assets				
Cash and Cash Equivalents	$ 13,884	**$ 15,972**	**$ 35,403**	**$ 58,328**
Short-term Investments	1,473	**4,455**	**2,455**	**3,951**
Accounts Receivable	7,547	**8,526**	**9,560**	**10,523**
Inventories	792	**1,289**	**1,630**	**2,057**
Deferred Income Taxes	457	**1,605**	**1,708**	**1,818**
Prepaid Expenses and Other CA	3,930	**3,564**	**4,032**	**4,500**
Total Current Assets (CA)	28,083	**35,412**	**54,788**	**81,177**
Property, Plant & Equipment	11,650	**14,383**	**43,895**	**46,569**
Excess of Cost over Net Assets of Acquired Business	3,698	**3,698**	**3,698**	**3,698**
Accumulated Amortization of Excess Cost	(1,449)	**(1,701)**	**(1,953)**	**(2,205)**
Other Assets	1,070	**1,297**	**4,631**	**4,820**
Total Assets	43,052	**53,089**	**105,059**	**134,059**
Liabilities and Equity				
Current Liabilities				
Accounts Payable and Other CL	6,919	**9,036**	**11,487**	**14,791**
Notes Payable	608	**632**	**620**	**626**
Current Maturities of Long-term Debt	634	**132**	**517**	**1,054**
Total Current Liabilities (CL)	8,161	**9,800**	**12,624**	**16,471**
Long-term Debt and Capital Lease Obligations	203	**0**	**24,523**	**21,716**
Other Liabilities	396	**405**	**418**	**430**
Total Liabilities	8,760	**10,205**	**37,565**	**38,618**
Equity				
Common Stock	87	**86**	**96**	**102**
Paid-in Capital	36,130	**35,164**	**46,938**	**56,955**
Currency Translation Adjustment	(75)	**(88)**	**(103)**	**(101)**
Retained Earnings (Deficit)	(1,850)	**7,722**	**20,564**	**38,485**
Total Equity	34,292	**42,884**	**67,495**	**95,441**
Total Liabilities and Equity	43,052	**53,089**	**105,059**	**134,059**

Table 11
Osteotech, Inc.
Annual Cash Flow Model
($ in thousands)

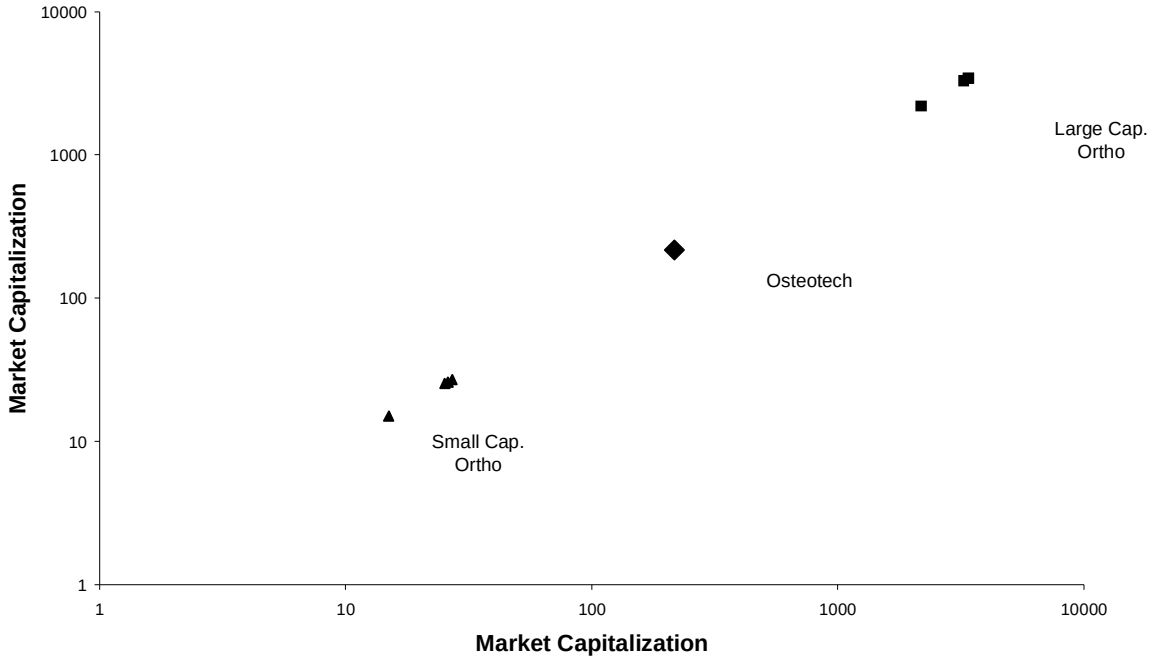
	1997	1998E	1999E	2000E
Cash from Operating Activities				
Net Income	$ 5,686	**$ 9,571**	**$ 12,841**	**$ 17,919**
Reconciliation of Net Income to Net Cash				
Depreciation and Amortization	2,065	**2,855**	**4,249**	**6,125**
Deferred Income Taxes	268	**(1,148)**	**(102)**	**(108)**
Changes is Assets and Liabilities				
Accounts Receivable	(1,329)	**(979)**	**(1,033)**	**(963)**
Inventories	(84)	**(497)**	**(341)**	**(427)**
Prepaid Expenses and Other CA	1,760	**366**	**(468)**	**(468)**
Accounts Payable and Other Liabilities	1,001	**2,117**	**2,451**	**3,304**
Cash Provided (Used) by Operating Activities	9,367	**12,286**	**17,596**	**25,382**
Cash from Investing Activities				
Capital Expenditures	(5,385)	**(5,336)**	**(33,509)**	**(8,547)**
Change in Investments	514	**(2,982)**	**2,000**	**(1,496)**
Increase (Decrease) in Other Assets	(231)	**(227)**	**(3,334)**	**(189)**
Cash Provided (Used) by Investing Activities	(5,102)	**(8,545)**	**(34,843)**	**(10,232)**
Cash from Financing Activities				
Proceeds from Issuance of Common Stock	3,110	**4,034**	**11,784**	**10,023**
Repurchase of Common Stock		**(5,000)**		
Change in Notes Payable	(47)	**24**	**(12)**	**6**
Change in Long-term Debt	(756)	**(705)**	**24,908**	**(2,270)**
Increase (Decrease) in Other Liabilities	0	**9**	**12**	**13**
Cash Provided (Used) by Financing Activities	2,307	**(1,638)**	**36,693**	**7,772**
Effect of Exchange Rate Changes on Cash	22	**(13)**	**(15)**	**2**
Increase (Decrease) in Cash and Equivalents	6,594	**2,089**	**19,431**	**22,924**
Cash and Equivalents Beginning of Period	7,290	**13,884**	**15,972**	**35,403**
Cash and Equivalents End of Period	13,884	**15,972**	**35,403**	**58,328**

Figure 23
Osteotech, Inc.
Valuation of Orthopedic Cohorts



Source: Maxxess by Fidelity; First Call; William Blair & Company, L.L.C. estimates

Figure 24
Osteotech, Inc.
Orthopedic Stock Market Capitalizations
($ in millions; log scale)



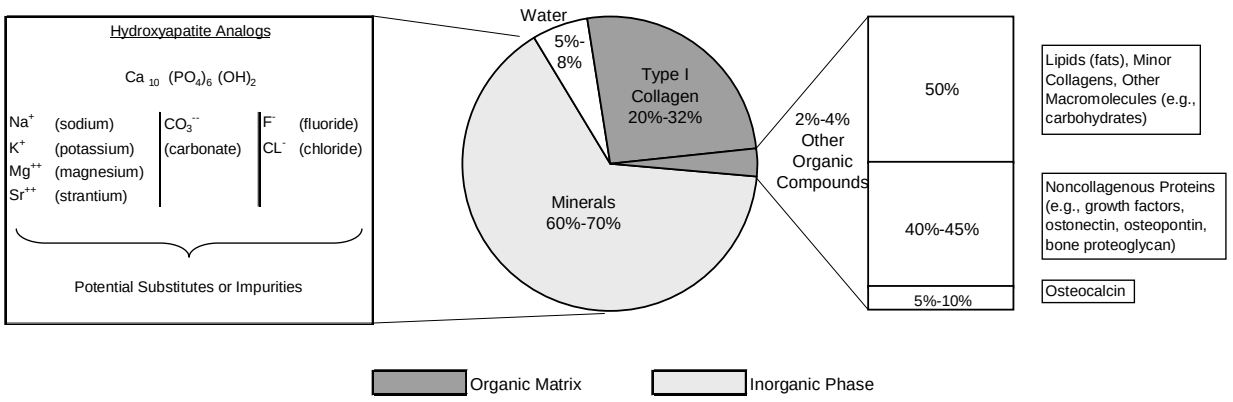
Source: First Call; Masses by Fidelity; William Blair & Company, L.L.C. estimates

Appendix A: Basics of Bone Biology

Bone Composition

The human body contains 206 bones. Bone is a complex, living, and constantly changing material made up of 60%-70% minerals (inorganic phase), 22%-35% organic compounds (organic matrix) and 5%-8% water. The variability in bone composition reflects site and function, age of the individual, diet, and certain diseases. Figure 25 illustrates the overall composition of bone, which is discussed in more detail below. The periosteum (a fibrous membrane that surrounds bone) and blood vessels permeate bone to provide oxygen, nutrients, biochemical molecules, and cells. Also, within the central cavity of long bones lie the hematopoietic precursor cells that form the cellular constituents of blood.

Figure 25
Osteotech, Inc.
Composition of Bone



Source: "Orthopaedic Basic Science"; William Blair & Company, L.L.C. estimates

Inorganic Phase

Sixty to seventy percent of bone is made up of minerals—mostly a type of calcium phosphate in a form called hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$], or hydroxyapatite analogs. The minerals form crystals that are 20-80 nanometers (nm) long and 2-5 nm thick in mature bone, arranged in a plate-like structure; the crystals are smaller in immature bone. As shown in figure 25, the hydroxyapatite in bone may contain many impurities, such as fluoride, potassium or carbonate. These may modify a bone's physical or biological properties, and often are necessary for normal function; impurities also may reflect an individual's diet (e.g., fluoride).

Organic Matrix

As shown in figure 25, 20%-32% of bone is a matrix of organic compounds, a scaffold over which the mineral phase is laid. This matrix is about 90% type I collagen. The other 10% contains approximately 50% noncollagenous proteins and 50% other types of macromolecules, such as lipids (fats), and carbohydrates (sugars). The protein portion contains growth factors—cytokines, proteoglycans, osteonectin, and osteopontin. Osteocalcin is the most common protein, making up 10%-20% of the noncollagenous portion. This protein is made by osteoblasts (see below) and appears to participate both in attracting osteoclasts (see below) and regulating mineralization.

Collagen is a low-solubility protein in the form of a triple helix. Type I collagen in bone is a semirigid molecule 300 nanometers long made of three protein chains, each about 1,000 amino acids in length. Collagen molecules align next to each other in a staggered fashion to form fibrils, which then form groups to form collagen fibers. This staggered structure contains gaps, "holes," or "pores," where the mineralization is likely to begin.

Types of Bone

Above the molecular level, bone can be structured in different ways, both microscopically and macroscopically. Microscopically, the collagen fibers can be arranged in a nonoriented manner, called *woven* bone, or they can be oriented in layers, called *lamellar* bone. Woven bone is more immature, and is found in embryos, newborns, the metaphysis (growth region of bone), or bone fracture calluses (where bone growth occurs to heal bone fractures). Lamellar bone is mature bone that begins to form about one month after birth, and comprises most of the bone in the body by age four. At the macroscopic level, bone is differentiated into spongy bone, called *cancellous* or *trabecular* bone, or compact, dense bone, called *cortical* bone. The cancellous bone has a remodeling (see below) rate of 5 to 10 times that of cortical bone. Conversely, cortical bone is four times denser than cancellous bone. Cancellous bone typically is located on the end of long bones and in the middle of the vertebral bones. Cortical bone is located along the length of long bones and the outside of vertebral bones, and typically accounts for 80% of the bone in an adult human.

Bone Cells

There are two types of cells involved in bone growth—those that grow bone (*osteoblasts* and *osteocytes*) and those that resorb bone (*osteoclasts).* The cells that form bone, osteoblasts and osteocytes, are essentially the same, the major difference being that osteoblasts are on the surface of the bone and osteocytes are located within the bone matrix. Osteoblasts and osteocytes are derived from the same pluripotent, mesenchymal osteoprogenitor stem cell that also can produce chondroblasts and fibroblasts, the cells that produce cartilage and tendons. In contrast, osteoclasts appear to be differentiated from the hematopoietic precursor cells that also differentiate into macrophages, the scavenging white blood cells that engulf and digest foreign bodies. Osteoblasts produce the type I collagen that forms the major component of the organic bone matrix, as well as producing other proteins and substances that induce mineralization. Osteoclasts are the cells responsible for resorbing old bone that is replaced by new bone—a process called remodeling—as discussed below.

Bone Growth and Turnover (Remodeling)

Bone remodeling is the process by which bone is regenerated or regrown. First, the mineral phase is removed and the organic matrix is metabolized, and second, the new matrix is laid down and remineralized. This process is cell-mediated, meaning that it is performed by the bone cells (osteoblasts and osteoclasts), not simply through biochemical processes. Although osteoclasts first must remove the old bone, this process actually is initiated by the osteoblasts. They must first contract from the bone surface and release a collagenase to remove surface collagen, allowing osteoclasts to access the underlying mineralized bone matrix. An osteoclast attaches itself to bone, it seals off a pocket called the subosteoclastic space, into which it releases enzymes that lower the pH level enough to dissolve the mineral phase and activate other enzymes designed to metabolize the organic matrix. After the materials have been resorbed, then the osteoblasts lay down a new organic matrix consisting predominantly of collagen, which then is remineralized with hydroyapatite. It is interesting to note that as osteoclasts break down the bone matrix, they release growth factors and other substances that stimulate bone growth, potentially providing a feedback loop that balances the resorption with bone growth.

Appendix B: Bone Grafting Materials and Bone Growth Enhancers

When possible, surgeons often employ the patient's own bone (autogenous bone graft) harvested at either the surgical site or from another site, usually from the top of the hip (iliac crest) if morselized bone is needed. Using autogenous bone graft is considered the "gold standard"; however, there often are considerable problems with using autograft.

Potential problems associated with the use of autogenous bone fall into four categories: failure of the "gold standard," donor-site morbidity, insufficient donor material, and metabolic hindrances for individual patients. First, the "gold standard" fails up to 35% of the time—i.e., not achieving the necessary bone growth—even with some form of fixation device. Second, if one must harvest the patient's own bone from the iliac crest, this requires a second surgery, as well as the associated cost and time. Also, in perhaps 25%-30% of the cases, there is pain or other morbidity at the donor site. Some patients who have had surgery complain that the donor site pain is worse than the original pain for which they were treated. Third, there may not be enough donor material, due either to previous graft harvests, the patient's needing more tissue than is available from his own body, (for example, in the case of a multilevel spine fusion or removal of a large tumor), or simply that the patient's own bone quality is insufficient, which is especially true in older individuals. Fourth, individual patients may have other conditions that can slow down or prevent fusion, including smoking, osteoporosis, or diabetes.

To address these shortcomings, surgeons use base allograft transplants, demineralized bone material such as Grafton® DBM, synthetic bone graft materials, and other bone growth stimulators. A variety of approaches have been and are under development. These can be divided into 6 groups: human allografts (such as those supplied by Osteotech), processed bone from animals (xenografts), synthetic grafts, cellular approaches (e.g., bone growth factors), electrical stimulation, or ultrasound.

Bone Grafts

Various bone graft materials have a combination of three different properties that allow them to enhance new bone growth and/or fusion. The material can be osteogenic, osteoinductive, or osteoconductive. *Osteogenic* means that the material contains cells that can form bone and can differentiate into bone-forming cells. For example, healthy autografts obviously contain viable bone or bone precursor cells, as does bone marrow, which can be added to grafting materials. *Osteoinductive* means that the material will induce differentiation or growth. This induction may be biological or chemical, but it also could be mechanical or physical. *Osteoconductive* refers to a material that provides a scaffold or matrix that allows and supports in growth of bone cells, blood vessels, and bone. Table 5 summarizes the bone growth properties of various materials.

Autografts have the greatest market share, accounting for more than 50% of procedures. This percentage illustrates two points. First, the other products have gained a significant level of acceptance, and there still is significant room to grow. The cost to the hospital for bone graft material other than autograft is about $800 per procedure, or between $500-$600 for the supplier, after subtracting the commission paid to the independent representatives. This means that the current potential value worldwide for bone grafts is estimated to be about $790 million, with about one-half of this in the United States and about one-quarter in Japan.

In addition to their use in the spine, bone graft materials also are used for other orthopedic applications, such as total joint replacement and revision, as well as in skull or maxillofacial procedures. However, use in the spine still is greatest, with 45% of the total number of procedures in the United States (see table 2).

Allografts

Allograft bone material is derived from processed human donor tissue. For allografts, donor screening and rigorous testing of donor tissue is critical to ensure that infectious diseases are not transferred. Allograft bone can be preserved by either freezing or freeze-drying, and this should occur as soon after harvest as possible to maintain the necessary physical and biological properties. Bone for freezing is brought to -70° to -196°C, and it can be stored for up to five years without a reduction in mechanical properties. Freeze-drying is more effective at reducing both the possibility for infection and an immune response (i.e., rejection) from the recipient. The bone is dehydrated under a vacuum and can be preserved in this vacuum indefinitely. Processed bone also is sterilized, either with gamma radiation or ethylene oxide, which appears to reduce the osteoinductivity and mechanical properties. Overall, however, many studies have shown good results with allografts. By decalcifying (demineralizing) allografts, a demineralized bone matrix (DBM) is formed, which causes a lower immune response. In addition, it appears that some of the bone growth factors that exist in the extracellular matrix are preserved and made accessible, thus enhancing osteoinduction. Despite processing techniques, xenografts often still induce an immune response, even if only a mild one, and their use therefore is declining in favor of human tissue and synthetics.

An important characteristic of allograft tissue is that it is remodeled or incorporated into new bone. This is a cell-mediated activity, with the cells that normally eliminate bone (osteoclasts) and the cells that form new bone (osteoblasts) actively performing this process. Also, certain forms of allografts (specifically, specially made demineralized bone matrix), also have better handling characteristics than even natural bone because they come in putty or gel forms that are better-suited for use during surgery

Xenografts

Xenograft material is derived from animals. Like allografts, xenografts require donor screening and rigorous testing of donor tissue, which is critical for ensuring that infectious diseases are not transferred. There has been a great deal of concern recently about cross-species infections, especially because many of these types of infections are not well-known, well-understood, or tested for. This often has limited the use of xenografts, particularly in new indications. As with allografts, xenograft tissue is remodeled or incorporated into new bone.

Synthetic Grafts

There are a variety of synthetic bone graft materials with various properties, including hydroxyapatite, bioglass, collagen, and calcium sulfate. Hydroxyapatite, like that supplied by Interpore, is either granular or in block form, is only osteoconductive, and resorbs slowly, if at all. Interpore is working with Quantic Medical to add superconcentrated platelets, ideally from the individual patient, to its material during surgery to impart osteoinductive properties. In addition, Interpore has introduced a more-resorbable material in Europe. Bioglass currently is used only in periodontal surgery. However, some of its properties make it a potentially better synthetic. It is both osteoinductive and conductive without an additive, and resorbs more quickly, potentially in a cell-mediated way. Collagen and calcium sulfate provide some osteoconductivity alone, but with better resorption than hydroxyapatite.

Competitors

The major competitors of autografts are the tissue banks, either within an institution or regional not-for-profits. Osteotech is the largest commercial supplier of bone graft material, with 56% of the commercial market, followed by GenSci, another allograft supplier with 18% and Interpore, a maker of the synthetic material hydroxyapatite, also with 18% share (see figure 9).

Cellular Approaches

Many cellular approaches are being investigated to induce bone growth, from bone growth factors, to developmental proteins, to precursor, or osteoprogenitor, cells. Bone growth factors stimulate or induce bone growth, so they obviously have potential in both trauma and fusion spinal applications. The major growth factors currently being pursued are bone morphogenetic proteins (BMPs) that are part of the human transforming growth factor b (TGF-b) superfamily of proteins, but there also are proteins from other families, nonhuman-derived proteins, and smaller peptides. Other firms are pursuing proteins or other molecules involved earlier in the developmental process of cells. These include the first characterized LIM mineralization protein (LMP-1) and Indian Hedgehog protein. Finally, a few companies are pursuing extracting, concentrating, or cloning specific osteogenic or osteoinductive cells.

Human TGF-b BMPs

Currently, the most-important growth factors of interest are BMPs derived from humans. In both animal and human clinical trials, these have been shown to increase both the rate and quality of bone growth and fusion. Six of the seven human BMPs discovered are related to each other in the TGF-b superfamily. These can be grouped into three sets, with one molecule in each set pursued commercially (see table 15). Sofamor Danek Group is pursuing BMP-2 though its collaboration with the Genetics Institute (see below). Interpore is seeking to commercialize BMP-3 (osteogenin), and Stryker Biotech is proceeding with BMP-7 (OP-1) through its collaboration with Creative Biomolecules (CBMI). Only 0.1 % of bone proteins by weight are BMPs, and BMPs have effects on cells other than bone and cartilage. Therefore, there are some regulatory concerns regarding the concentration used, as well as the carrier or mechanism for placing and keeping the BMPs in the same site within the body. Companies are investigating various bone graft materials, as well as other materials (e.g., Hedrocel™ cage) as carriers.

Other Growth Factors

In addition to human BMPs, companies are pursuing other growth factors. For example, Sulzer Orthopedics Biologics is developing a mixture of bovine-derived BMPs, Ne-Osteo. Sulzer is testing the product both alone and in conjunction with the BAK fusion cage of Sulzer Spine-Tech, and believes that a mixture will be better than a single factor and that a product extracted from cows will be much less expensive than a recombinant human protein. Obviously, there are regulatory, as well as perceptual, issues regarding animal-extracted versus recombinant proteins. Another growth factor currently being pursued is not a protein, but a water-soluble peptide one-tenth its size—bone cell stimulating factor, or BCSF™, from Allelix Pharmaceuticals and Millennium Biologix. There is some clinical evidence to date of bone growth stimulation with this molecule, but much more scientific work needs to be done.

Cell Differentiation and Development

At least two approaches currently are being tested regarding influencing the developmental pathway of cells prior to differentiation—LMP-1 and Indian Hedgehog. LMP-1 is a zinc-binding nuclear matrix protein that appears to govern the development and “cell fate” of cells that become osteoblasts. Using this approach likely would require a “gene therapy” procedure; however, it appears that only a few cells need to be activated at a local site, overcoming two of the earlier drawbacks of gene therapy (i.e., need for many cells and a systemic effect). Additionally, this approach seems to work with any cells, in contrast with the mesenchymal stem-cell approach discussed below. Hedgehog proteins (Sonic, Indian, and Desert) also are involved early in cell differentiation. Specifically, the Indian Hedgehog appears to be most involved in bone and cartilage cell differentiation. Ontogeny, a biotechnology firm, is pursuing this molecule in the bone area. Both of these approaches probably are at least six years from the market due to product development timelines and U.S. regulatory approval.

Cells

In addition to growth factors, one can envision using stem cells directly, or cells that produce osteoinductive factors. One of the most direct ways to do this is to harvest a patient's own (autologous) bone marrow, but this is an additional, painful procedure. Quantic Medical, working with Interpore, is taking an analogous but less-painful approach by developing a system to superconcentrate platelets during surgery from the patient's own blood. Quantic has shown an increased rate of bone formation using this approach. Osiris Therapeutics uses the patient's own bone marrow, but separates the mesenchymal stem cells (cells intended to differentiate into bone formation and resorption cells), then significantly expands the number of cells in culture. This has the advantage of both reduced invasiveness and pain from bone marrow collection, as well as some data showing improved results over fresh bone marrow or autografts. However, it requires time to expand the number of cells and could be costly.

Electrical Stimulation

Human and animal clinical studies have shown that electrical stimulation reduces the time and increases the eventual success rate or spinal fusion. The appropriate currents seem to be between 5 and 25 microamps, which either can be delivered through pulsed electromagnetic fields or applied directly. The increase in successful fusions has been reported to be 20%-30%; use of electrical stimulation can add about $4,000-5,000 to the incremental cost of a case. Examples of commercial electrical stimulation products are the OsteoGen™ surgically implanted bone growth stimulator for long-bone, non-union fractures, SpF® internal spinal fusion stimulator, EBI Bone Healing System® from EBI (Biomet), and the Spinal-Stim® external stimulator from Orthofix that now is being distributed by Sofamor Danek.

Ultrasound

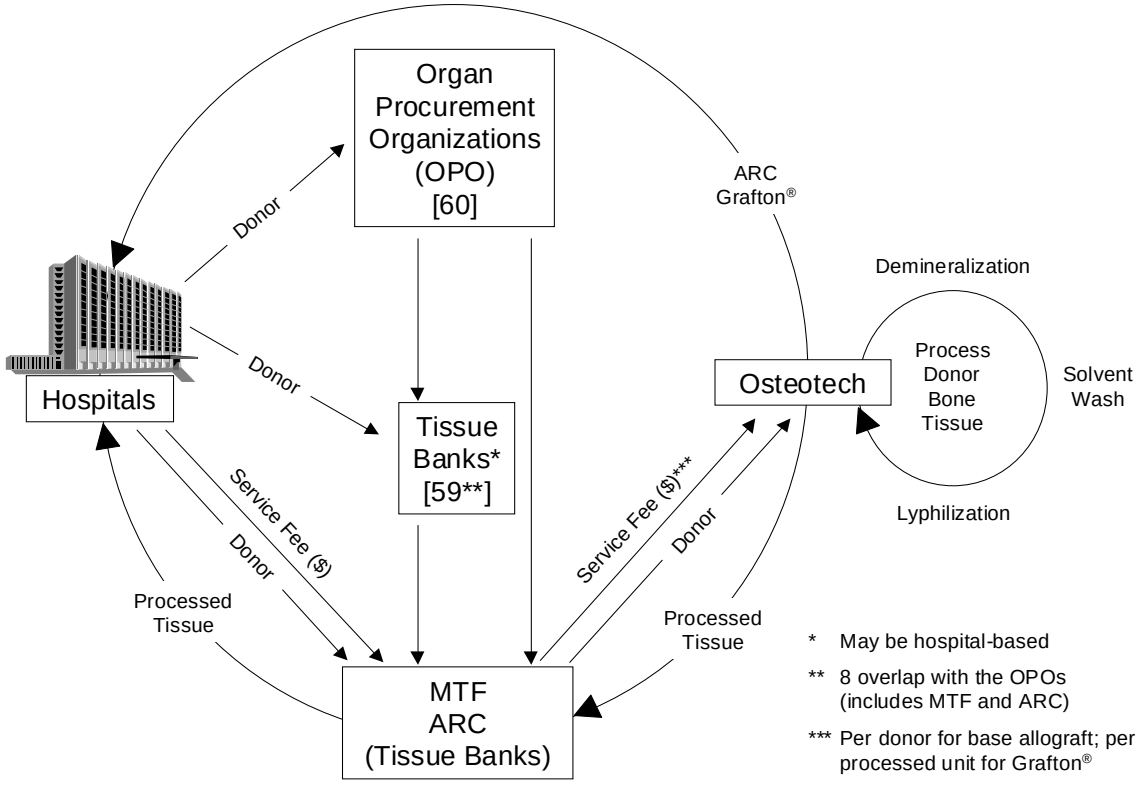
Lastly, another possible approach to biological enhancement is low-intensity pulsed ultrasound. This approach has been shown to accelerate fracture healing, such as nonunion fractures. In 1994, the FDA approved the SAFHS (sonic accelerated fracture healing system) for adults with small fractures in the lower arm or leg. However, while this might be valuable in long-bone fractures, there is only limited data available in the largest potential market, the spine.

Appendix C: Bone Donor Procurement and Allograft Bone Distribution Processes

Domestically, Osteotech does not procure any donors of bone, nor does it distribute processed allograft bone or bone products, with one exception—Grafton® DBM, distributed for the American Red Cross Tissue Services (ARC). These procurement and distribution activities are performed exclusively by the company's not-for-profit clients, the Musculoskeletal Transplant Foundation (MTF) and the ARC.

As figure 26 illustrates, human bone tissue donors are procured from a hospital either by a regional organ procurement organization (OPO) that typically handles whole organs; a local tissue bank, which may be hospital-based or independent; or a national or superregional tissue bank, such as the MTF or ARC. There are 60 OPOs and 59 tissue banks in the United States, with 8 organizations overlapping. Typically, a hospital will have a contract with a specific organization for various types of tissues (see discussion of recent HCFA regulation below. OPOs and tissue banks also have contracts or other arrangements whereby they provide specific types or quantities of bone tissue to one another after procurement.

Figure 26
Osteotech, Inc.
Allograft Process Flow



Source: Osteotech, Inc.; MTF; ARC; AATB; industry interviews; William Blair & Company, L.L.C. analysis

Procurement and processing also involves screening and testing of the donors for infectious diseases. This is discussed in appendix E, "Allograft Safety."

After procurement and testing, the donated material then is shipped to the processing site, which for the MTF and ARC is the Osteotech facility. At the processing site, the bone tissue is processed according to a donor-specific requisition provided by either MTF or ARC. Once processed, the base allograft and Grafton® DBM then is tested and returned to either the MTF's or ARC's own distribution facility, except for ARC Grafton® DBM which Osteotech stores and drop-ships to the appropriate hospital. The MTF and ARC then provide the tissue to their client hospitals, which pay them a processing fee. MTF and ARC also pay Osteotech a processing fee, which for base allograft is paid per donor and for Grafton® DBM is paid for each packaged unit.

Unlike whole organs, which are viewed a national resource, bone tissue may be used at the same facility from which it was procured if there is a specific need. This is made possible by the careful tracking and isolation of each donor throughout the entire process. Each donor is kept as a separate "lot." Not only is this useful to allow for the donor's use by the originating institution, but it also ensures the necessary tracking and accountability regarding safety.

Recent HCFA Regulation

Recently, the Health Care Financing Administration (HCFA) announced a regulation intended to increase donation, specifically of whole organs. Under this regulation, all hospitals must have a relationship with an OPO and tissue bank (if the OPO does not handle tissue), and each potential donor must be referred. The objective of this approach is to increase organ donations by 20%. Anecdotally, donations have increased 40% in Pennsylvania, where a similar law has been in effect since 1995. In total, nine states already have similar laws, including Arizona, Florida, Illinois, Maryland, New Jersey, New York, North Carolina, Pennsylvania, and Tennessee. These regulations are not intended to interfere with existing contractual relationships, but to prevent donors from "slipping through the cracks," such as when an OPO is contacted for whole organs, but no tissue bank is contacted for bone or eye tissue.

Appendix D: Regulation of Human Tissue

U.S. National Organ Transplant Act (NOTA)

The National Organ Transplant Act (NOTA) was passed in 1984 with the intention of formalizing a national transplant system. This system was to be overseen by the U.S. Department of Health & Human Services and was made up of a network of not-for-profit Organ Procurement Organizations (OPOs). The original act allowed for voluntary membership and adherence to policies, but in 1986 this provision was amended through the Omnibus Reconciliation Act, which required adherence to the policies for institutions receiving Medicare and Medicaid reimbursement. However, the final rules were not published until March 1998, and now have been put into effect.

Organ purchases or sales were prohibited by Title II of NOTA, which established criminal penalties for doing so. However, NOTA still allows for the charging of service fees by all parties involved, including the hospital, OPOs, tissue banks and third-party processors like Osteotech.

FDA Regulations

The FDA currently does not have a distinct regulatory approach for human tissue, although it recently has proposed such an approach (see proposed rule discussed below). Some human tissue products were regulated as medical devices (e.g., heart-valve allografts, corneal lenticles, and dura mater); others as biological drugs (e.g., somatic cell-therapy products) and still others as banked human tissue (e.g., bone allografts and reproductive cells). In 1993, the FDA used the regulatory authority granted to it by the Public Health Service Act (PHSA) to require HIV and hepatitis testing for all human tissue other than reproductive tissue.

Currently, the allograft products that Osteotech produces are regulated as banked human tissue, and therefore are not subject to the premarketing procedures of the FDA (e.g., 510[k], PMA). This was confirmed for Grafton® DBM in particular on the basis of a ruling in August 1995 that declared it within the scope of the Interim Rule on Human Tissue Intended for Transplantation, as the glycerol excipient used has no biological effect. In fact, glycerol first was listed as GRAS (Generally Recognized As Safe) in 1961 and reclassified as a multipurpose food substance in 1977, long before its use in Grafton® DBM. As banked human tissue, Osteotech's allograft products still are required to be manufactured under specific quality-assurance procedures—e.g., good tissue practices and good manufacturing practices—as well as meet the safety and quality criteria designated by the FDA and American Association of Tissue Banks (AATB), such as HIV testing (see appendix E).

Proposed FDA Rule: Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-based Products

The FDA proposed this rule in May 1998 to establish a unified approach for human cellular and tissue-based products; written comments on the rule were to be collected through August 12, 1998. The FDA considered five issues in developing the proposed regulatory framework: 1) how transmission of infectious disease occurs and can be prevented; 2) how to prevent contamination while maintaining the integrity and function of the various products through various controls of handling, processing and manufacturing; 3) how to address concerns regarding a product's safety and efficacy; 4) how to label products for proper use, and consequently, what kinds of promotion would be permissible; and 5) how to interact with and monitor the industry.

Certain types of cellular and tissue-based products are not covered by the proposed rule. These include: transfusable blood products, which the FDA regulates under a different, more-suitable scheme; whole organs and minimally manipulated bone marrow, which already is regulated by the Health Resources Services Administration; and products that are extracted or secreted, such as collagen, growth factors, and cytokines, which the FDA believes already are best covered under different regulatory approaches because they have different issues regarding safety, efficacy, and manufacturing. Also, ancillary products used for processing or storage are not covered, but already are covered elsewhere. Lastly, xenografts are not covered, as they raise other complex public health and safety issues in addition to those raised by human tissue.

Table 13 summarizes the proposed FDA regulations regarding human tissue. Minimally processed allografts such as Grafton® DBM only should require screening for infectious diseases and adherence to good tissue practices. Extensively processed allografts, allografts combined with a noncellular or nonallograft component, allografts used for a different function, or those with a systemic effect all likely would require a PMA.

Table 13
Osteotech, Inc.
Proposed FDA Unified Approach to Regulate Human Tissue

Type of Tissue	Regulatory Process
Autogenous transplant during same surgical procedure	None required
Minimally processed allografts for same function	Infectious disease screening and good tissue practices
Allograft for different function	PMA generally required
Allograft with systemic effect	PMA generally required
Allograft combined with noncellular or nonallograft component	PMA generally required
Extensively processed allograft	PMA generally required

Source: *U.S. Federal Register*; FDA; industry interviews; William Blair & Company, L.L.C. analysis

European Regulations

Currently, companies involved in human tissue allografts in Europe are subject to a variety of national regulations. However, there is some pressure to develop pan-European regulations that may regulate human tissue along with medical devices.

Some European medical-device industry associations have developed a broad classification system around which a regulatory framework would be built. This system would classify human tissue into the following five groupings:

1) Minimally processed tissue, such as frozen or freeze-dried skin, bone or cardiovascular tissue.

2) Processed tissue, such as demineralized bone with or without a GRAS carrier or excipient (e.g., Grafton® DBM).

3) Tissue-engineered autografts, such as autologous chondrocytes cultured to replace cartilage.

4) Tissue-engineered allografts that have been cultured, such as those use in skin grafting.

5) Extracted or recombinant protein material, such as collagen or growth factors.

At this point, it appears that Europewide human tissue regulations may take some time to be developed, agreed upon, and enacted.

French Proposal for Human Tissue Regulations

Since Osteotech recently made a major foray into Europe through France, it is important to understand the French perspective on human tissue regulations. Also important to note is the fact that France has been willing to impose stricter measures unilaterally for high-risk medical devices than those agreed upon by the broader European Union. Consequently, we have outlined the criteria that the French government recently has circulated regarding human tissue regulation below.

- Establish a system for authorizing and inspecting organizations involved in the procurement, processing, storage, and distribution of human tissue. This system also would include rules regarding safety, such as mandatory screening criteria and processing procedures, as well as traceability of allografts.

- Create a pan-European database of authorized products and services.

- Assure that any medical device containing human tissue be subject to regulations for both human tissue *and* medical devices.

- Exclude whole organs, as they typically are transplanted shortly after removal with minimal processing and storage.

- Delineate specific ethical standards.

Note that the proposed criteria would at this point provide for a regulatory framework similar to that faced by Osteotech in the United States, depending on the specific interpretations and rules that eventually are derived (e.g., in relation to what constitutes a device versus human tissue, or what specific ethical standards are agreed upon).

Appendix E: Allograft Safety

Screening by Tissue Banks

Bone is donated like any other organ by consenting individuals and their families. Before a donor is accepted, the person must be screened and tested; consequently, most accepted donors are healthy and relatively young people that die in accidents or by unexpected illnesses, like heart attacks. To screen potential donors, medical and social histories are taken and reviewed, and in-vitro diagnostic tests are performed. First, the cause of death must be known. Persons with any medical history of diseases such as AIDS, hepatitis, or cancer are ruled out, as well as those that have been exposed to toxic substances or who have a history of high-risk behavior. Table 14 details the complete list used by the MTF of donor exclusions on the basis of medical or social history. Finally, if any donor candidate tests positive for relevant infectious diseases, such as HIV, hepatitis, or syphilis, they are not accepted. For example, the MTF was the first bone tissue organization to test for HIV using PCR on every donor and for routine screening requiring both PCR and immunodiagnostic tests to find either HIV DNA or HIV antibodies.

Table 14
Osteotech, Inc.
Donor Exclusions Based on Medical or Social History

Past Medical and Social History: Potential donors with a history of any of the following conditions are excluded from donation:

- AIDS, AIDS-Related Complex
- High risk for AIDS as defined by U.S. Public Health Services
- Hepatitis B or C; unexplained jaundice
- Intravenous drug abuse
- Malignancy, except basal and squamous cell carcinoma and carcinoma in-situ of the uterus and cervix
- Infectious diseases, e.g., tuberculosis, leprosy, rabies, malaria, syphilis, septicemia or long-term bacterial or fungal infections
- Slow viral diseases, e.g., Epstein-Barr, Creutzfeldt-Jakob Disease (CJD)
- Autonomous diseases, e.g., rheumatoid arthritis, myasthenia gravis, lupus
- Neurological and/or demyelinating diseases, e.g., amyotrophic lateral sclerosis, multiple sclerosis, muscular dystrophy
- Dementia, including senile dementia, cerebral arteriosclerosis and Alzheimer's disease
- Diseases of bone and connective tissues
- Diseases of unknown etiology
- Exposure to toxic chemicals/metals, e.g., lead, mercury, Agent Orange
- Use of human-derived pituitary growth hormone
- Recent (within 4 weeks) immunization against: measles, rubella, mumps, polio, or yellow fever

Current Medical Status: Potential donors with any of the following existing medical conditions are excluded from donation:

- Positive tests for the following infectious deseases: HIV 1 & 2, HTLV-I Ab, HbsAg, HCV Ab, RPR
- Active infection, e.g., meningitis, encephalitis, tuberculosis, typhus, measles, mumps, rubella, chicken pox, herpes, pneumonia, and/or other viral/fungal/bacterial diseases
- Active unexplained immune-system disorders
- Active system infections
- Clinical manifestations of bacterial or viral infections, e.g., elevated WBC except where related to trauma, high fever unexplained by CNS injury, septic IV site, septic decubiti, open skin lesions, unexplained rashes, or purulent wounds

Source: Musculoskeletal Transplant Foundation; William Blair & Company, L.L.C. analysis

In addition to ruling out patients to prevent disease transmission, Osteotech's client tissue banks also screen for potential donors more than 50 years old or with histories of diseases, such as osteoporosis, obesity, alcoholism, or diabetes that could affect the quality and long-term performance of the bone. For MTF, these donations must be approved by its medical director, technical director, and director of quality assurance. To make that decision, MTF uses bone-density analysis and compares the potential donor with established standards.

Strict procedures are followed in bone recovery. All bone must be recovered within 24 hours of death (12 hours if the body was not refrigerated within the first 12 hours). The bone tissue itself is recovered in sterile environments by surgeons and specially trained technicians. Once the tissue is recovered, it is maintained in aseptic environments and processed in Class 10 clean (aseptic) rooms. Maintaining an aseptic environment throughout the process eliminates the need for secondary sterilization at the end of the process, thus further helping to maintain the integrity of the tissue.

Viral Inactivation by the Bone Demineralization Process

The viral inactivation ability of the bone demineralization process used by Osteotech has been validated by an independent third party. The first series of experiments validated the process for demineralizing the bone powders used to make Grafton® DBM, consisting of pulverized bone powder with a particle size of 100-500 mm. The company is planning to have its process validated for all its allograft bone products by the end of 1998.

The bone demineralization process consists of four steps, three of which have distinct viral inactivation properties. The first step is to strip cortical bone of soft tissue, cut it into the various sizes required, and then rinse and clean it thoroughly. The second step is the demineralization itself. The third step is a solvent treatment that is completely rinsed off. The fourth, and last, step is the lyophilization of the demineralized bone. To make the various Grafton® DBM products, additional processing occurs to combine the bone powders with the glycerol carrier; however, this additional processing does not contribute to the viral inactivation properties.

Table 15 shows the viral inactivation for each step of the process for each viral type in a spiked sample, as validated by Quality Biotech in Camden, New Jersey. Note that this is based on a log scale—a 1 would represent a 1 in 10 chance that a virus survives, a 2 would represent 1 in 100, and 9.46 (for total HIV inactivation) means 1 in 2,884,031,503. The ">" sign means that the virus that could be loaded into the sample was brought to undetectable levels.

Table 15
Osteotech, Inc.
Viral Inactivation in Demineralization Process

	Virus				
Process Step	**HIV**	**HBV (DHBV)**	**HCV (BVD)**	**CMV**	**Polio**
Demineralization	>5.23	>3.70	>4.25	>2.92	>5.99
Solvent Wash	>4.23	>3.70	>3.15	>3.32	>3.72
Lyophilization	None	ND	1.77	None	2.30
Total Inactivation	>9.46	>7.40	>9.07	>6.24	>12.01

Source: *Contemporary Orthopedics*; William Blair & Company, L..L..C. analysis

Low Odds of an Adverse Event

When the screening and diagnostic steps are combined with the validated viral inactivation characteristic of the bone tissue process, the odds of infectious disease transmission should approach a remarkably small probability. Table 16, on the next page, puts these odds into perspective. One is much more likely to have a fatal reaction to the general anesthesia used during the surgery (1 in 5,000 surgeries) or even getting HIV from a blood transfusion (1 in 444,000 transfusions).

Table 16
Osteotech, Inc.
Estimated Odds of Adverse Events

Adverse Event	Estimated Odds of Occurrence
Having Your Car Stolen	1 in 159 (annual)
Fatal Motorcycle Accident	1 in 1,000 (annual)
Fatal Reaction to General Anesthesia	2 in 10,000 (surgeries)
Fatal Running Accident	1 in 10,000 (annual)
HIV Transmission From a Blood Transfusion	1 in 440,000 (tranfusions)
Dying From Falling out of Bed	1 in 513,142 (annual)
Freezing to Death	1 in 780,938 (annual)
Contracting the AIDS Virus From an Allograft Bone Transplant	1 in 1,670,000* (transplants)
Transmission of the HIV Virus From a Grafton® Transplant	<1 in 2,800,000,000**

* Before PCR to detect HIV DNA

Source: MTF; *Contemporary Orthopedics*; William Blair & Company, L.L.C. analysis

Appendix F: Glossary

360° Fusion. Anterior plus posterior fusion.

510(k). A 510(k) is a premarketing notification submitted to the FDA to demonstrate that a medical device is as safe and effective as and substantially equivalent to a legally marketed device that was on the U.S. market prior to 1976. The Food and Drug Modernization Act of 1997 allows the FDA to reclassify new devices on the basis of their risk.

AANS. American Association of Neurological Surgeons.

AAOMS. The American Association of Oral and Maxillofacial Surgeons.

AAOS. The American Academy of Orthopaedic Surgeons.

AAP. American Academy of Periodentology.

AGF. Autologous growth factors.

ALIF. Anterior lumbar interbody fusion. Placement of bone or cages between vertebrae from an anterior approach.

ALP (Alkaline Phosphatase). An enzyme that removes phosphate groups from organic compounds at an alkaline pH. It is found in high concentrations in matrix vesicles that are about to form new bone and is a good indicator of bone formation. It is also secreted into the serum by osteoblasts and is used as a diagnostic marker for increased osteoblastic metabolic activity.

Allograft. A graft transplanted between two different individuals of the same species (e.g., from cadavers).

Alveolar bone. Bone that develops around the roots of the teeth to hold them firmly in place.

Alveolar ridge. The part of the jawbone structure that surrounds and holds the roots of the teeth.

Anterior. Front-facing.

ARC. American Red Cross Tissue Services.

Arthrodesis. An operation to stiffen a joint, usually through bone fusion.

Asceptic. Sterile.

Autocrine. Cell messengers produced by the cell itself that regulate the expression of genes. Denoting self-stimulation through cellular production of a factor and a specific receptor for that factor.

Autograft. A bone graft using the patient's own bone, usually harvested from the iliac crest of the hip.

Bacteriostatic. Stopping or inhibiting the growth of bacteria.

BMP. Bone morphogenic protein. Proteins found in demineralized bone matrix that participate in bone formation.

Bone graft. Bone transplanted from a donor site to a recipient site.

Bovine. From or related to a cow.

BVD. Bovine diarrheal virus.

Cancellous bone. Bone with a spongy or lattice-like structure. Also called trabecular bone.

Cervical vertebrae. The seven segments of the vertebral column located in the neck between the skull and the rib cage.

Chemotaxis. Movement of cells or organisms in response to chemicals.

Chondroblast. A cell that produces cartilage.

Chondrogenesis. Formation of cartilage.

CMV. Cytomegalovirus. Any of a group of viruses that cause cellular enlargement.

Cortical bone. Compact/dense bone.

CPT codes. Current procedural terminology. A set of codes published by the American Medical Association that are used for reimbursement purposes in the health care and insurance industries.

Cytokine. Hormone-like, low-molecular-weight proteins secreted by many different cell types that regulate the intensity and duration of immune responses and are involved in cell-to-cell communication.

Degenerative disc disease. A deterioration in the structure or function of the disc.

Demineralization. A loss or decrease in minerals in the body or individual tissues, especially bone.

DHBV. Duck hepatitis B virus.

Diaphysis. Shaft of long bone.

Disc. A tough, elastic structure located between the adjacent surfaces of the vertebrae forming the connection between these segments and allowing for cushioning, movement, and shock absorption.

Disc Degeneration Grading (Nachemson, A.L. definition)

Grade I. A shiny, gelatinous nucleus pulposus is easily delimited from the annulus fibrosus, which is free of macroscopic ruptures or discoloration.

Grade II. Macroscopic changes are present only in the nucleus pulposus, which is somewhat more fibrous, but still clearly distinct from the intact annulus fibrosus.

Grade III. Macroscopic changes are present in both nucleus pulposus and annulus fibrosus. The nucleus pulposus is more fibrotic, but still soft. The boundary between nucleus pulposus and annulus fibrosus is no longer distinct. Isolated fissures are found in the annulus fibrosus.

Grade IV. Severe macroscopic changes exist in both nucleus and annulus. Fissures and cavities are present in both the nucleus pulposus and annulus. Marginal osteophytes are often found on adjacent vertebrae.

Discectomy. Surgical removal of intervertebral disc that typically is abnormally protruding (herniated).

Dorsal. Pertaining to the back.

DRG. Diagnostic related groups. A system of codes used to group patients by diagnosis for reimbursement purposes.

Ectopic. Out of place.

EGF. Epidermal growth factor. A cytokine that stimulates epithelial cell proliferation.

Endochondral. Within a cartilage or cartilaginous tissue.

Endochondrial ossification. Formation of bone by the replacement of calcified cartilage.

Endosseous implants. A dental implant that is inserted into the jawbone to replace the root portion of teeth. They usually are shaped like a screw or cylinder and are made of metal, metal-covered ceramic, or ceramic material.

Epiphysis. Bone that is distinct from the diaphysis, separated by a layer of cartilage.

Excipient. An inert substance used as a diluent or vehicle for a drug.

FGF. Fibroblast growth factors. A family of at least nine related proteins that regulate the proliferation, differentiation, and function of a variety of cell types. They also play a role in promoting tissue formation.

Fibroblast. Cells capable of producing collagen for connective tissue, such as tendons.

Fibronectin. A glycoprotein found in the extracellular matrix important for the attachments, and therefore the movement, of cells. High-molecular-weight multifunctional glycoproteins found on cell-surface membranes and in blood plasma and other body fluids. They are thought to function as adhesive, ligand-like molecules, which stimulate the clearance of debris from blood plasma.

Fracture callus. Bone growth at site of a fracture.

Glycerol. A syrupy, sweet, colorless, or yellowish liquid derived from fats and oils as a byproduct of the manufacture of soaps and fatty acids.

Guided bone regeneration. Using a membrane to guide bone growth.

HBV. Hepatitis B virus. Inflammation of the liver, marked by jaundice and fever, usually transmitted by injection of infected blood or by use of contaminated needles.

HBC. Hepatitis C virus.

Hedgehog proteins (Sonic, Indian, Desert). Group of proteins involved in developmental and regeneration processes. Indian hedgehog has been shown to be involved in bone formation and homeostasis.

Hemostatic. Stopping the flow of blood.

Herniated disc. An abnormal protrusion of an intervertebral disc.

HIV. Human immunodeficiency virus.

HPO. Human periosteal cells.

Hydroxyapatite. A naturally occurring mineral that closely resembles the crystal lattice of bones and teeth.

ICD-9 codes. International classification of diseases. A classification system that groups related disease entities and procedures for the reporting of statistical information.

IDE. Investigational device exemptions. These allow for new devices to be tested in human clinical trials.

Idiopathic. A disease of unknown origin.

IGF. Insulin-like growth factor.

Iliac crest. The highest part of the pelvis on each side.

Laminectomy. Removal of posterior bone (laminae) in the spine that surrounds the spinal chord. Often done in conjunction with a discectomy and spinal fusion.

Lateral. Pertaining to the side.

Ligaments. A band of fibrous tissue connecting two or more bones or cartilages.

Lumbar vertebrae. The vertebrae, usually five in number, located in the lower region of the back.

Lyophilization. The process of isolating a solid substance from solution by freezing the solution and evaporating the ice under vacuum.

Mandibular. Lower jawbone.

Maxillary. Upper jawbone.

Maxillofacial. Pertaining to the jaws and face.

Medial. Relating to the middle.

Metaphyseal fracture. Fracture located at the metaphysis.

Metaphysis. Conical bone located between the diaphysis and the epiphysis.

Mitogenesis. Transformation of a cell.

MTF. Musculoskeletal Transplant Foundation.

NASS. North American Spine Society.

NTBN. National Tissue Bank Network.

NOTA. National Organ Transplant Act.

OPO. Organ procurement organization.

Osteoblast. A bone-forming cell.

Osteoclast. A cell that aids in the absorption and removal of bone.

Osteoconductive. Providing a suitable matrix or scaffold through which bone will form.

Osteogenesis. Formation of bone.

Osteogenic. Directly providing stem cells capable of making bone.

Osteoinductive. Inducing bone-cell differentiation and growth through biological, chemical, mechanical, or physical means.

Osteomyelitis. Inflammation involving bone.

Osteoporosis. A reduction in the quantity of bone.

Osteoprogenitor cells. Undifferentiated cells that give rise to osteoblasts and osteocytes.

Paracrine. Relating to a kind of hormone function in which the effects of the hormone are restricted to the local environment.

PCR. Polymerase chain reaction.

PDGF. Platelet-derived growth factor.

Pedicle. A short, thick bone that projects backward from the body of a vertebra, which connects with the lamina on either side.

Pedicle fixation. Attaching to the pedicle.

PLIF. Posterior lumbar interbody fusion.

PMA. Premarket approval. Premarket approval is the process of scientific and regulatory review to ensure the safely and effectiveness of all Class III (high risk) and some Class II (moderate risk) devices. An approved premarket approval application is, in effect, a license granted to the applicant for marketing a particular medical device, on the basis of clinical trials proving both safety and efficacy.

Polio virus. An inflammatory process involving the gray matter of the nerve cord.

Posterior. Rear-facing.

Proteoglycan. Molecules found in connective tissue that combine amino acids—the building blocks of proteins—with polysaccharides or sugars.

Pseudoarthrosis. A new, or false, joint arising at the site of an ununited fracture.

PTH. Parathyroid hormone.

PTHrP. Parathyroid hormone-related protein.

Remodeling. A cyclical process by which bone maintains the same shape and size through sequential resorption and formation of a small amount of bone at the same site.

Scoliosis. An abnormal lateral curvature of the spine.

Sinus lift. A bone graft procedure to expand the width and height of the bone within the implant site in order to create a new sinus floor necessary for the implant.

Skeletogensis. Bone formation.

Spondylolisthesis. Anterior displacement of a lumbar vertebra on the vertebra below, or sacrum.

Spondylosis. A stiffening or fixation of the vertebrae.

Spinal cord. The part of the central nervous system contained within the spinal canal, running from the base of the skull to the lower back.

Spinal fusion. An operative procedure in which the disc between two adjacent vertebrae is removed and then the two vertebrae are fused together.

Spinal stenosis. A narrowing or stricture of the spine.

TBI. Tissue Bank International.

TGF-b. Transforming growth factor-b. A family of proteins that can function as regulators for cell adhesion and migration, stimulators of the expression of extracellular matrix proteins and integrins, modulators of important immune functions, attractants of cells by chemotaxis, and inhibitors of the growth of many cell types.

Thoracic vertebrae. The twelve segments of the vertebral column between the neck and the abdomen that are attached to the ribcage.

Tissue bank. Repository and distribution center for donated human tissues such as bone.

Trabecular bone. Bone with a spongy or lattice-like structure. Also called cancellous bone.

Urethral sphincter augmentation. Replacement or reconstruction of the urethral sphincter to restore urinary continence in men with severe stress urinary incontinence after radical retropubic prostatectomy.

Vertebra. Any of the single bones or segments of the spinal column.

Xenograft. A graft transferred from an animal of one species to one of another species.