# SYNTHETIC BONE GRAFTING PRODUCTS

## MARKET RATIONALE

Today, 45% of all general orthopedic and 95% of all spinal fusions include the use of bone graft material for reconstruction. Of these cases, a conservative estimate of autograft procedures accounted for 60% (240,000) of all procedures, allograft was utilized in 30% (120,000 procedures) and synthetic grafting material being utilized in 10% (40,000 procedures). Historically, however, autograft procedures are complex since they require surgeons to harvest the graft from the patient and then shape the tissue by hand, using standard operating room instruments prior to implanting the tissue. This requirement increases the amount of surgery time in addition to donor site morbidity, blood loss, increased hospital stay, and the increased potential for infection. These factors have significantly increased the attractiveness of utilizing synthetic materials for bone grafting in General Orthopedic and Spinal indications.

## MARKETING & DISTRIBUTION

### U.S. Bone Grafting Overview

Defects in bones and other human tissue can be caused by a variety of sources including trauma, congenital defect, infectious disease, cancer, and other metabolic conditions. The prevalent method used by neuro and orthopaedic surgeons to repair and promote the healing of defective tissue is surgery, principally through the use of surgical implants. When considering a surgical procedure for general orthopaedic and spinal tissue repair, surgeons and patients are favoring synthetic treatment options. A short review of the current treatment options is detailed below:

#### Autograft

In order to overcome the drawbacks to the use of metallic implants and xenograft tissue, surgeons have increasingly turned to autograft procedures. Autografts, in contrast to metals, are "osteoconductive," but can be "osteoinductive" as well. Historically, however, autograft procedures are not as easy to perform since grafting often required the surgeon to harvest the graft from the patient and then shape the tissue by hand, using standard operating room instruments prior to implanting the tissue. This requirement not only increases the total surgery time, but can also place the patient at risk since the surgeon must harvest the tissue from a second site on the patient's body.

#### Allograft

Since the introduction of allograft implants, more surgeons chose allograft procedures to treat musculo-skeletal and other tissue defects. The patients may enjoy the benefits of an implant that promotes bone growth and better healing without having to undergo the potentially risky second surgery to obtain autograft tissue for transplant. However, with

the recent knowledge of increased potential for viral and bacterial disease transmission, surgeons prefer more and more autografts or sterile synthetic implants since they share the same convenience and ease-of-use advantages as metals and autogaft without their drawbacks.

**Xenograft**

While used in other parts of the world, the use of xenograft, or animal tissue, is not prevalent in the United States other than for heart valve replacements and urinary incontinence. Bone tissue from animal origin is banned in a number of European countries. The primary reason for the minimal use of xenografts is the increased risk of an adverse reaction. Current processing techniques are unable to completely remove the proteins that initiate an adverse immunological response. An additional reason for limited use of xenograft tissue in the United States is the perceived risk of disease transmission, such as mad cow disease.

**Synthetic**

Synthetic grafts such as hydroxyapatite and tri-calcium phosphate offer limitless availability. Alone, synthetics can impart two significant advantages: 1) providing minimal immediate structural support; and 2) providing zero potential for viral or bacterial disease transmission. The synthetic osteoconductive scaffold provides an appropriate environment in which bone cells and bone morphogeneic proteins (BMPs) can adhere and proliferate. The ability to control the reabsorption rate and the 3-dimensional structure is critical to the speed of incorporation and remodeling; a more porous, lower density construct provides greater surface area exposure for supply of nutrients, vascularization, and bony in-growth.

## U.S. MARKET SIZE AND GROWTH RATE

The bone grafting market can be broken down into a number of distinct segments, including spinal, oral-maxillofacial and general orthopaedic. Table I. contains an estimate for 1999 on these segments in the United States that can be addressed through the use of bone grafting implants:

**Table I. Estimated Allograft Utilization for 1999**

| Market | Total Procedures | Bone Grafting Procedures | Bone Grafting Revenues | Penetration |
|---|---|---|---|---|
| **Spinal** | 400,000 | 120,000 | $144 million | 30% |
| **Oral-Maxillofacial** | 67,900 | 15,000 | $4.5 million | 2.2% |
| **General Orthopaedic** | 485,000 | 125,000 | $100 million | 36% |

Bone and synthetic grafting material are the most common tissue for transplant procedures, second only to blood. The overall market in the United States for the use of bone graft materials has grown considerably over the last several years, with allograft and synthetics increasing 14-fold between 1985 and 1996, and now accounts for one-third of bone graft procedures performed in the United States.

Autograft, allograft and synthetic implants are commonly used to induce fusion in spinal procedures. However, although autograft is concerned the "gold standard," donor site morbidity, increased hospital stay, and the increased potential of infection have significantly increased the utilization of allograft material and research into synthetic options. It is estimated that the U.S. bone grafting market including synthetics is mirroring the US spine fusion market with a conservative growth rate of 15% annually, which should lead to a estimated market size in excess of $675 million by 2007. Table II. displays the U.S. projected market value by year for allograft and synthetic bone grafting materials in millions.

**Table II. - Historical and Projected U.S. Market for Allograft and Synthetic Grafting Material**

| DESCRIPTION | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 |
|---|---|---|---|---|---|---|---|---|---|---|
| **Allograft** | 144 | 166 | 190 | 219 | 252 | 290 | 333 | 383 | 440 | 507 |
| **Synthetic** | 48 | 55 | 63 | 73 | 84 | 97 | 111 | 128 | 147 | 169 |
| **Total In Millions** | 192 | 221 | 254 | 292 | 336 | 386 | 444 | 511 | 587 | 675 |

Numerous health care analysts believe that there will continue to be an increase in the use of surgical implants for repair and healing, and in particular, synthetic implants used for orthopaedic and spinal applications. These reasons include:

- The aging of the baby boom generation will result in a greater percentage of the population requiring bone grafting products.
- As life expectancies increase overall, the need for bone grafting products will increase
- High volume surgical procedures requiring biologic products for a large and rapidly growing domestic and international market.
- Advanced processing techniques and specifications for synthetic grafting products that provide a significant clinical advantage.
- As patients and their families become increasingly proactive in determining the nature of the health care they receive and as they increasingly use the Internet to research health care alternatives, pressure will increase on medical providers for more natural healing alternatives.
- Increasing awareness of the safety and benefits of synthetics that provide an increase in the acceptance by surgeons and patients.
- Advancements and innovations in graft design increase the acceptance of synthetic implants by surgeons and patients.

# TABLE III: CURRENT BONE GRAFT SUBSTITUES

| Commercially Available Product | Vitoss | Cortoss | OrthoBlast | DynaGraft | ProOsteon 500R | Grafton | OsteoSet | AlloMatrix |
|---|---|---|---|---|---|---|---|---|
| **Composition** | Tri-Calcium Phosphate | Terpolymer resin with combeite glass-ceramic reinforcing particles | Heat sensitive copolymer with cancellous bone chips and DBM | Heat sensitive copolymer with DBM | Coral HA Composite | Demineralized bone matrix (DBM) combined with glycerol | Surgical grade calcium sulfate | DBM with surgi grade calcium sulfate powde |
| **Commercially Available Forms** | Granular or block | Granular or block | Injectable paste or putty | Injectabel gel, matrix or putty | Granular or block | Gel | Various sized pellets | Injectable or formable putt |
| **Claimed Mechanisms of Action** | Osteoconduction Bioresorabable | Osteoconduction Bioresorabable | Osteoconduction Bioresorabable Limited osteoinduction | Osteoconduction Bioresorabable Limited osteoinduction | Osteoconduction Bioresorabable | Osteoconduction Bioresorabable Limited osteoinduction | Osteoconduction Bioresorabable | Osteoconducti Bioresorababl Limited osteoinductio |
| **Burdens of Proof** | Case reports Animal studies | Case reports Animal studies | Case reports Animal studies Cell culture | Human studies Case reports Animal studies Cell culture | Human studies Case reports Animal studies | Human studies Case reports Animal studies | Human studies Case reports Animal studies | Case reports Animal studie Cell culture |
| **FDA Status** | Approved 510K | Approved 510K | Minimal manipulation Non-Regulated | Minimal manipulation Non-Regulated | Approved 510K | Minimal manipulation Non-Regulated | Approved 510K | Minimal manipulation Non-Regulate |
| **Marketed By** | OrthoVita independent reps | OrthoVita independent reps | GenSci independent reps | GenSci independent reps | Interpore Cross International | MTF / ARC | WMT | WMT |

# MARKETING STRATEGY

Berkeley Advanced Biomaterials synthetic product line was developed to meet the market demands to provide a synthetic material to enhance bone growth, remodeling, and fusion in orthopaedic and spinal procedures. Berkeley Advanced Biomaterials products will fulfill the following need:

1. **Sterile Synthetic Bone Graft** will fulfill the need for sterile, biocompatible implants composed of hydroxyapatite and tri-calcium phosphate that provides the natural environment for new bone in-growth with out the risk of viral or bacterial disease transmission.

**Sterile Synthetic Bone Graft:**

**Target Market:** The sterile synthetic bone graft product will be marketed and sold to any physician specializing in general, trauma, oncology and/or orthopaedic spine surgery, who wishes to utilize a synthetic scaffold for bone incorporation, due to the concern of disease transmission. In addition, the sterile synthetic bone graft product will also be targeted at physicians who wish to utilize this product in conjunction with autograft or allograft as a graft extender.

**Competitive Edge:** The advantage of providing a sterile synthetic bone grafting material is four-fold: 1) Berkeley Advanced Biomaterials will be able to provide a reliable option to physicians and patients who wish to eliminate the possibility of a viral or bacterial disease transmission, which is possible with allograft; 2) Since the composition of the product is commercially available in limitless supply, supply will not be limited to the anatomical and physiological limitations critical for processing allograft tissue; 3) Synthetic grafting materials will eliminate donor site morbidity, reduce hospital stay, and eliminate the potential of bacterial or viral infections; and 4) The synthetic product can be produced in various specifications regarding porosity, particle size, and a calculated reabsorption rate.