
BONE-GRAFT SUBSTITUTES: *FACTS, FICTIONS & APPLICATIONS*



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A REALITY CHECK

It is estimated that more than 500,000 bone-grafting procedures are performed annually in the United States, with approximately half of these procedures related to spine fusion. These numbers easily double on a global basis and indicate a shortage in the availability of musculoskeletal donor tissue traditionally used in these reconstructions. (Figure 1)

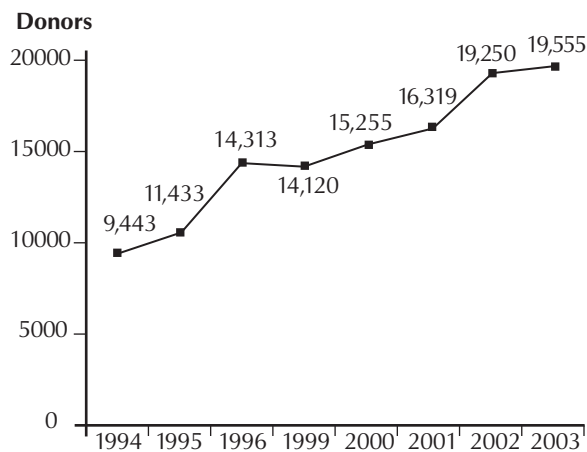


Figure 1: U.S. trends in musculoskeletal tissue donors. Source: AATB Annual Survey

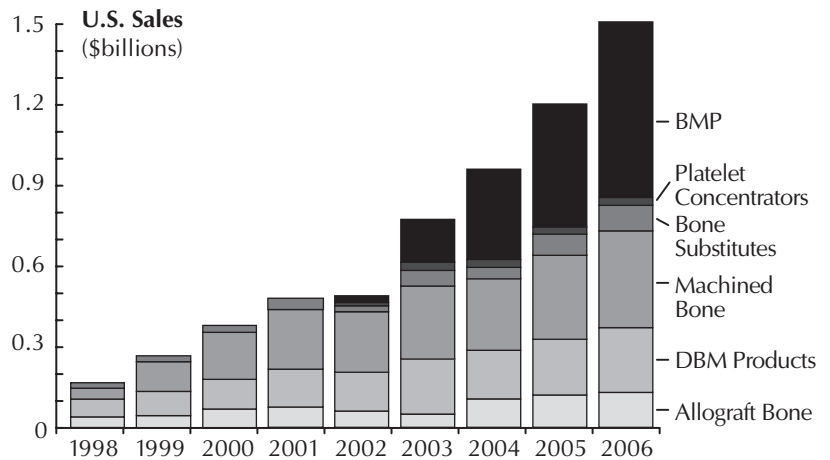


Figure 2: U.S. sales of bone graft and bone substitutes Source: Orthopedic Network News

This reality has stimulated a proliferation of corporate interest in supplying what is seen as a growing market in bone replacement materials. (Figure 2) These graft alternatives are subjected to varying degrees of regulatory scrutiny, and thus their true effectiveness in patients may not be known prior to their use by orthopaedic surgeons. It is important to gain insight into this emerging class of bone-substitute alternatives.

THE PHYSIOLOGY OF BONE GRAFTING

The biology of bone grafts and their substitutes is appreciated from an understanding of the bone formation processes of Osteogenesis, Osteoinduction and Osteoconduction.

Graft Osteogenesis: The cellular elements within a donor graft, which survive transplantation and synthesize new bone at the recipient site.

Graft Osteoinduction: New bone realized through the active recruitment of host mesenchymal stem cells from the surrounding tissue, which differentiate into bone-forming osteoblasts. This process is facilitated by the presence of growth factors within the graft, principally bone morphogenetic proteins (BMPs).

Graft Osteoconduction: The facilitation of a bone healing process into a defined passive trellis structure.

All bone graft and bone-graft-substitute materials can be described through these processes.

While fresh autologous graft has the capability of supporting new bone growth by all three means, it may not be necessary for a bone graft replacement to have all three properties inherently in order to be clinically effective. When inductive molecules are locally delivered on a scaffold, ultimately mesenchymal stem cells are attracted to the site and are capable of reproducibly inducing new bone formation provided minimal concentration and dose thresholds are met. In some clinical studies, osteoinductive agents have been shown to potentially perform superiorly.

However, bone marrow aspirate applied to osteoconductive scaffolds are still reliant on the local mechanical and biological signals in order to ultimately form bone. For this reason, these materials are typically used as an adjunct in order to retain efficacy equivalent to autograft.

Similarly, osteoconductive materials work well when filling non-critical size defects that would normally heal easily. However, in more challenging critical size defects, either fresh autologous bone graft or osteoinductive agents appear necessary for healing.

BONE AUTOGRAFTS

Fresh autogenous cancellous and, to a lesser degree, cortical bone are benchmark graft materials that allograft and bone substitutes attempt to match in *in vivo* performance. They incorporate all of the mentioned properties, are harvested at both primary and secondary surgical sites, and have no associated risk of viral transmission. Furthermore, they offer structural support to implanted devices and, ultimately, become mechanically efficient structures as they are incorporated into surrounding bone through creeping substitution. The availability of autografts is, however, limited and harvest is often associated with donor-site morbidity.

BONE ALLOGRAFTS

The advantages of bone allograft recovered from deceased donor sources include its ready availability in various shapes and sizes, avoidance of the need to sacrifice host structures, and no donor-site morbidity. Bone allografts are distributed through regional tissue banks and by most major orthopaedic and spinal companies. Still, the grafts are not without controversy, particularly regarding their association with the transmission of infectious agents, a concern virtually eliminated through tissue-processing and sterilization. However, uncontrolled and unvalidated processing and irradiation protocols may alter graft biomechanical and biochemical properties. It is critical to know your tissue bank provider to ensure their processing and preservation methods do not negatively alter the biomechanical and biochemical properties of the tissues intended for a particular clinical use. A comparison of properties of allograft and autograft bone is shown in Figure 3. Often, in complex surgical reconstructions, these materials are used in tandem with implants and fixation devices. (Figure 4)

Bone Graft	Structural Strength	Osteo-Conduction	Osteo-Induction	Osteogenesis
Autograft				
Cancellous	No	+++	+++	+++
Cortical	+++	++	++	++
Allograft				
<i>Cancellous</i>				
Frozen	No	++	+	No
Freeze-Dry	No	++	+	No
<i>Cortical</i>				
Frozen	+++	+	No	No
Freeze-Dry	+	+	No	No
Demineralized Allogeneic Cancellous Chips	No	+	++	No

Figure 3: Comparative properties of bone grafts



Figure 4: (a) A 17-year old patient with osteosarcoma of the distal part of the femur with no extraosseous extension or metastatic disease. Following chemotherapy, (b) limb salvage with wide resection was performed. Femoral reconstruction with the use of an autogenous cortical fibular graft, iliac crest bone chips, morselized cancellous autograft and structural allograft combined with internal fixation. (c) Graft incorporation and remodeling are seen at 3 years. (d) Limb restoration is noted at 10 years following resection. (The intramedullary rod was removed at 5 years.)

BONE GRAFT SUBSTITUTES

The ideal bone-graft substitute is biocompatible, bioresorbable, osteoconductive, osteoinductive, structurally similar to bone, easy to use, and cost-effective. Within these parameters a growing number of bone alternatives are commercially available for orthopaedic applications, including reconstruction of cavitory bone deficiency and augmentation in situations of segmental bone loss and spine fusion. They are variable in their composition and their claimed mechanisms of action. A series of case examples demonstrate their mechanisms of action through the healing process. (Figures 5-8)

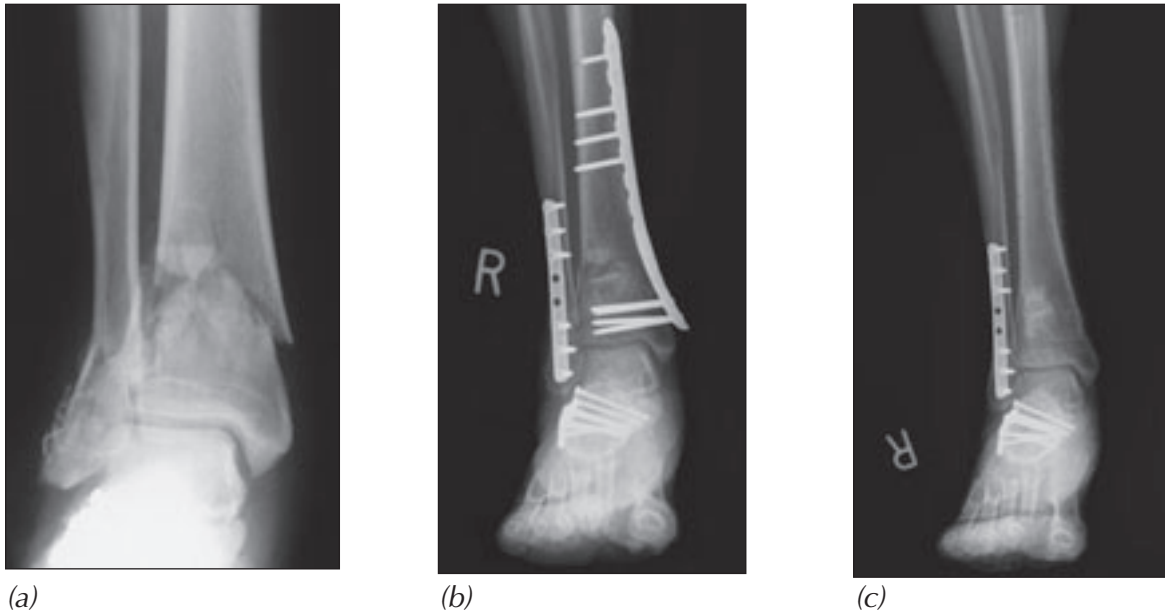


Figure 5: (a) A 61-year old male with a comminuted pylon fracture sustained in a motor vehicle accident. (b) After 2 months with an external fixator, definitive fixation of the tibia with a percutaneous injection of IGNITE® (Wright Medical Technology, Inc., Arlington, TN) graft to bridge the slow-healing fracture. (c) Two years post-op, the fracture is consolidated and the patient is ambulating pain-free.

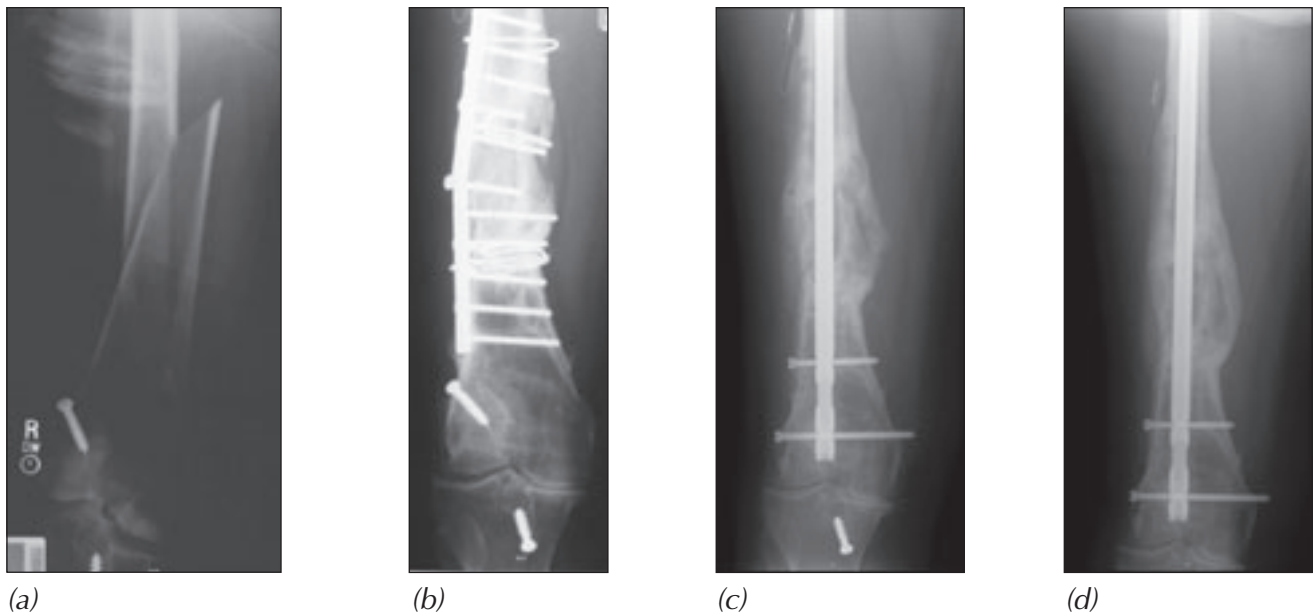


Figure 6: (a) A 58-year old obese female with a nonunion of the right femur after falling from a horse. Treatments included plating with cortical struts and DBM. (b) Nine months following third surgery the plate and several screws are broken. (c) Three months after treatment with IM rod fixation and OP-1® Implant (Stryker Biotech, Hopkinton, MA) she was full weight bearing, with full range of motion and pain free. (d) Nine months postoperative.

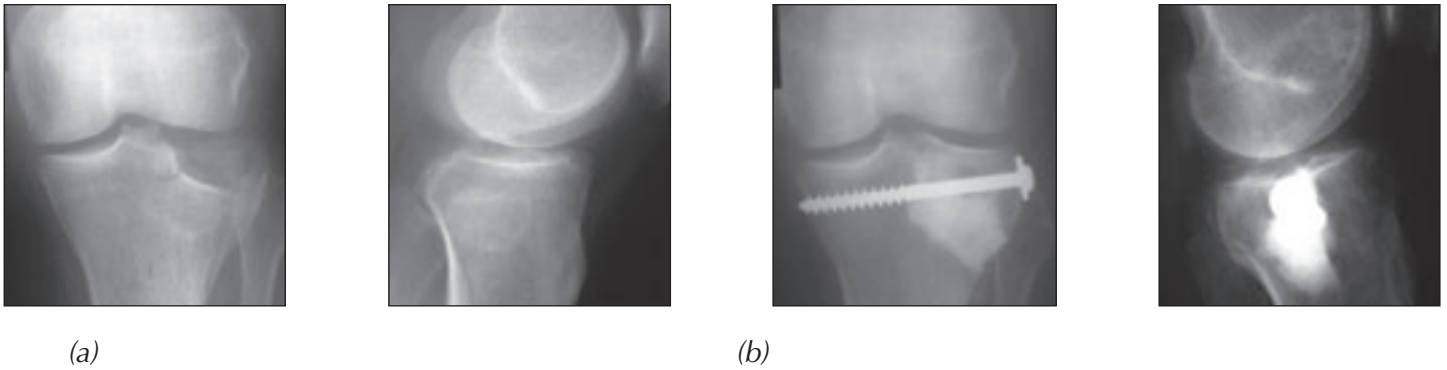


Figure 7: (a) AP and Lateral radiographs, 67-year old female with depressed fracture of the lateral tibial plateau. (b) AP and Lateral radiographs 12 months after ORIF with filling the defect with Norian® SRS® (Synthes USA, Paoli, PA). No loss of reduction of the plateau surface is noted, fracture completely healed.

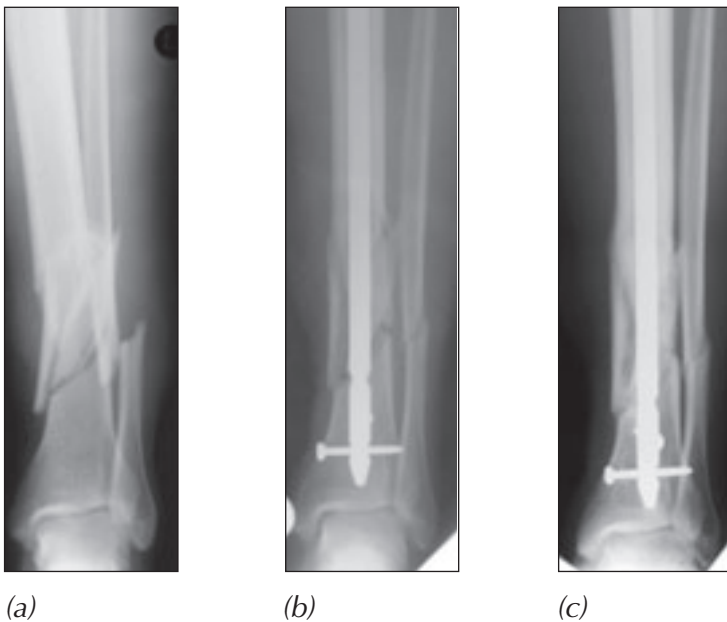


Figure 8: (a) A 29-year old male with a Grade III B oblique fracture of the distal tibia from a motorcycle accident. (b) Six weeks after being treated with an unreamed locked nail and INFUSE® Bone Graft (Medtronic Sofamor Danek, Memphis, TN). (c) Patient full weight bearing and radiographically healed 20 weeks post-operative.

BURDEN OF PROOF

It is reasonable to assume that not all bone-substitute products will perform the same. This presents a challenging choice for the orthopaedic surgeon. As a first principle, it is important to appreciate that different healing environments (e.g., a metaphyseal defect, a long-bone fracture, an interbody spine fusion, or a posterolateral spine fusion) have different levels of difficulty in forming new bone. For example, a metaphyseal defect will permit the successful use of many purely osteoconductive materials. In contrast, a posterolateral spine fusion will not succeed if purely osteoconductive materials are used as a stand-alone substitute. Thus, validation of any bone-graft substitute in one clinical site may not necessarily predict its performance in another location.

A second principle is to seek the highest burden of proof reported from preclinical studies to justify the use of an osteoinductive graft material or the choice of one brand over another. Whether it is more difficult to make bone in humans than it is in cell-culture or rodent models, with a progressive hierarchy of difficulty in more complex species, has not been clearly determined. Only human trials can determine the efficacy of bone-graft substitutes in humans as well as their site-specific effectiveness. In this latter context, surgeons should practice evidence based medicine and tailor treatment for patients based on the published medical literature and the levels of evidence claimed. (Wright JG, Swiontkowski MF, Heckman JD. *Introducing levels of evidence to the journal. J Bone Joint Surg Am.* 2003 Jan;85(1):1-3.)

BURDEN OF PROOF (Cont'd.)

A third principle requiring burden of proof specifically pertains to products that are not subjected to high levels of regulatory scrutiny, such as 100% demineralized bone matrix (DBM) or platelet gels containing “autologous growth factors”. Such products are considered to involve minimal manipulation of cells or tissue and are thus regulated as tissue rather than as devices, unless they are configured with an additive and then require 510(k) clearance. As a result, there is no standardized level of proof of safety and effectiveness required before these products are marketed and are used in patients. While these products may satisfy the technical definition of “*minimal manipulation*”, there is a risk that they will not produce the expected results in humans when there has been little or no testing in relevant animal models.

FUTURE

FDA approvals include the use of PMA approved rhBMP-2 (INFUSE® Bone Graft) as an autograft replacement in spinal fusion and treatment of open tibia fractures; rhBMP-7 (OP-1® Implant) is HDE approved as an autograft substitute for long bone nonunions; and rhBMP-7 (OP-1® Putty) is HDE approved as an alternative to autograft in compromised patients requiring revision posterolateral (intertransverse) lumbar spinal fusion, for whom autologous bone and bone marrow recovery are not feasible or are not expected to promote fusion. These clinical applications demonstrate impressive osteoinductive capacity and pave the way for broader clinical applications. Their methods of administration include direct placement in the surgical site, but results have been more promising when the growth factors have been administered in combination with substrates to facilitate timed-release delivery and/or provide a material scaffold for bone formation. FDA regulatory imperatives will continue to determine their availability. Their cost/benefit ratio will ultimately influence clinical use.

Further advances in tissue-engineering, “the integration of the biological, physical and engineering sciences”, will create new carrier constructs that regenerate and restore tissue to its functional state. These constructs are likely to encompass additional families of growth factors, evolving biological scaffolds and incorporation of mesenchymal stem cells. Ultimately, the development of *ex vivo* bioreactors capable of bone manufacture with the appropriate biomechanical cues will provide tissue-engineered constructs for direct use in the skeletal system.

TAKE HOME MESSAGE

- The increasing number of bone-grafting procedures performed annually in the U.S. has created a shortage of cadaver allograft material and a need to increase musculoskeletal tissue donation.
 - This has stimulated corporate interest in developing and supplying a rapidly expanding number of bone substitutes, the makeup of which includes natural, synthetic, human and animal-derived materials.
 - Fresh autogenous cancellous and, to a lesser degree, cortical bone are the benchmark graft materials, which ideally both allograft and bone substitutes should match in *in vivo* performance. Their shortcomings include limited availability and donor-site morbidity.
 - The advantages of allograft bone include availability in various sizes and shapes as well as avoidance of host structure sacrifice and donor-site morbidity. Transmission of infection, particularly the human immunodeficiency virus (HIV) has been virtually eliminated as a concern. The properties of the allograft should be confirmed with the tissue provider to ensure they correspond with their intended clinical use.
 - The ideal bone-graft substitute is biocompatible, bioresorbable, osteoconductive, osteoinductive, structurally similar to bone, easy to use, and cost-effective. Currently marketed products are variable in their composition and their claimed mechanisms of action. It is reasonable that not all bone-substitute products will perform the same.
 - FDA approvals for specific uses of recombinant human growth factors (rhBMP-2 (INFUSE® Bone Graft) and rhBMP-7 (OP-1® Implant and OP-1® Putty)) are based on demonstrated osteoinductive capacity in human trials. Other applications will likely emerge.
 - The orthopaedic surgeon has many choices for bone grafting. *Caveat emptor!* Selection should be based on reasoned burdens of proof. These include examination of the product claims and whether they are supported by preclinical and human studies in site-specific locations where they are to be utilized in surgery. It is imperative to appreciate the level of evidence claimed in the latter studies.
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Summary of typical bone-graft substitutes that are commercially available - 2007

Company	Commercially available product	Composition	Commercially available forms	Claimed mechanisms of action	Burdens of proof	FDA status
AlloSource	AlloFuse™	Heat sensitive copolymer with DBM	Injectable gel and putty	<ul style="list-style-type: none"> • Osteoconduction • Bioresorbable • Osteoinduction 	<ul style="list-style-type: none"> • Case reports • Animal studies • Cell culture 	• 510(k) cleared
Biomet/EBI/Interpore Cross	ProOsteon® 500R	Coral HA composite	Granular or block	<ul style="list-style-type: none"> • Osteoconduction • Bioresorbable 	<ul style="list-style-type: none"> • Human studies • Case reports • Animal studies 	• 510(k) cleared
	InterGro®	DBM in a lecithin carrier	Paste, putty and mix with coral/HA composite granules	<ul style="list-style-type: none"> • Osteoconduction • Bioresorbable • Osteoinduction 	<ul style="list-style-type: none"> • Case reports • Animal studies • Every lot tested for osteoinduction 	• 510(k) cleared
	BonePlast®	Calcium sulfate	Powder/fluid mixed with hardenable paste	<ul style="list-style-type: none"> • Osteoconduction • Bioresorbable 	<ul style="list-style-type: none"> • Case reports • Animal studies 	• 510(k) cleared
Exactech	Opteform®	DBM and cortical cancellous chips in gelatin carrier	Formable putty, syringeable cylinders and dry powder ready to be hydrated with blood or saline	<ul style="list-style-type: none"> • Osteoconduction • Bioresorbable • Osteoinduction 	<ul style="list-style-type: none"> • Human studies • Case reports • Animal studies • Every lot tested <i>in vivo</i> for osteoinduction 	• 510(k) cleared
	Optefil™	DBM suspended in gelatin carrier	Injectable bone paste, dry powder ready to be hydrated with blood or saline	<ul style="list-style-type: none"> • Osteoconduction • Bioresorbable • Osteoinduction 	<ul style="list-style-type: none"> • Human studies • Case reports • Animal studies • Every lot tested <i>in vivo</i> for osteoinduction 	• 510(k) cleared
	Optecure™	DBM suspended in a hydrogel carrier	Dry mix kit delivered with diluents and mix with patient's whole blood or autogenous bone	<ul style="list-style-type: none"> • Osteoconduction • Bioresorbable • Osteoinduction • Osteogenesis when mixed with autogenous bone graft 	<ul style="list-style-type: none"> • Animal studies • Every lot tested <i>in vivo</i> for osteoinduction 	• 510(k) cleared
	Optecure™ + CCC	DBM and CCC suspended in a hydrogel carrier	Dry mix kit delivered with diluents and/or mix with patient's whole autogenous bone	<ul style="list-style-type: none"> • Osteoconduction • Bioresorbable • Osteoinduction • Osteogenesis when mixed with autogenous bone graft 	<ul style="list-style-type: none"> • Animal studies • Every lot tested <i>in vivo</i> for osteoinduction 	• 510(k) cleared
	OpteMx™	HA/TCP biphasic combination	Granules, sticks, rounded wedges, wedges and cylinders in several sizes	<ul style="list-style-type: none"> • Osteoconduction • Bioresorbable • Compressive strength of 400psi • Osteogenesis and limited osteoinduction when combined with bone marrow aspirate 	<ul style="list-style-type: none"> • Human studies • Case reports • Animal studies 	• 510(k) cleared

Company	Commercially available product	Composition	Commercially available forms	Claimed mechanisms of action	Burdens of proof	FDA status
IsoTis OrthoBiologics	Accell Putty™	DBM putty	Injectable putty	<ul style="list-style-type: none"> Osteoconduction Bioresorbable Osteoinduction 	<ul style="list-style-type: none"> Human studies Case reports Animal studies Every DBM lot tested for osteoinduction 	<ul style="list-style-type: none"> 100% derived from DBM FDA clearance not required
	Accell Plus™	DBM plus reverse phase medium	Injectable putty	<ul style="list-style-type: none"> Osteoconduction Bioresorbable Osteoinduction 	<ul style="list-style-type: none"> Human studies Case reports Animal studies Every DBM lot tested for osteoinduction 	<ul style="list-style-type: none"> 510(k) cleared
	Accell TBM	Total bone matrix, 100% preformed	Various sized strips	<ul style="list-style-type: none"> Osteoconduction Bioresorbable Osteoinduction 	<ul style="list-style-type: none"> Human studies Case reports Animal studies Every DBM lot tested for osteoinduction 	<ul style="list-style-type: none"> 100% derived from DBM FDA clearance not required
LifeNet	Optium DBM®	DBM combined with glycerol	Formable putty and injectable gel	<ul style="list-style-type: none"> Osteoconduction Bioresorbable Osteoinduction 	<ul style="list-style-type: none"> Human studies Case reports Animal studies 	<ul style="list-style-type: none"> 510(k) cleared
	IC Graft Chambers®	DBM particles and cancellous chips	Lyophilized and provided in various sizes	<ul style="list-style-type: none"> Osteoconduction Bioresorbable Osteoinduction Designed to be used with blood, PRP or bone marrow to enhance DBM activity. 	<ul style="list-style-type: none"> Animal studies 	<ul style="list-style-type: none"> Regulated under CFR 1270 and 1271 as a human tissue and 510(k) cleared
	Cellect DBM®	DBM fibers and cancellous chips	Provided in a specialized cartridge	<ul style="list-style-type: none"> Osteoconduction Bioresorbable Osteoinduction Designed for the retention of osteoprogenitor cells 	<ul style="list-style-type: none"> Animal studies Case studies 	<ul style="list-style-type: none"> Regulated under CFR 1270 and 1271 as a human tissue and 510(k) cleared
	OraGraft®	Demineralized and mineralized cortical powder	Provided in various sized quantities	<ul style="list-style-type: none"> Osteoconduction Bioresorbable Osteoinduction 	<ul style="list-style-type: none"> Animal studies 	<ul style="list-style-type: none"> 100% DBM FDA clearance not required
Medtronic Sofamor Danek	INFUSE™ Bone Graft	rhBMP-2 protein on an absorbable collagen sponge	Freeze-dried, sterile powder and sponge in several sizes	<ul style="list-style-type: none"> Bioresorbable sponge Osteoinduction 	<ul style="list-style-type: none"> Human studies (Level I and Level III data) Case reports Animal studies 	<ul style="list-style-type: none"> PMA approved for fusion with spinal cage PMA approved for open tibia fractures with IM nail
	MasterGraft® Granules	Biphasic calcium phosphate	Granules	<ul style="list-style-type: none"> Osteoconduction Bioresorbable 	<ul style="list-style-type: none"> Animal studies 	<ul style="list-style-type: none"> 510(k) cleared
	MasterGraft® Matrix	Calcium phosphate and collagen	Compression resistant block	<ul style="list-style-type: none"> Osteoconduction Bioresorbable 	<ul style="list-style-type: none"> Animal studies 	<ul style="list-style-type: none"> 510(k) cleared
	MasterGraft® Putty	Calcium phosphate and collagen	Injectable putty	<ul style="list-style-type: none"> Osteoconduction Bioresorbable 	<ul style="list-style-type: none"> Animal studies 	<ul style="list-style-type: none"> 510(k) cleared

Company	Commercially available product	Composition	Commercially available forms	Claimed mechanisms of action	Burdens of proof	FDA status
MTF/Synthes	DBX®	DBM in sodium hyaluronate carrier	Paste, putty mix and strip	<ul style="list-style-type: none"> • Osteoconduction • Bioresorbable • Osteoinduction 	<ul style="list-style-type: none"> • Human studies • Case reports • Animal studies 	• 510(k) cleared
Orthovita	Vitoss®	100% β -TCP and 80% β -TCP/20% collagen	Putty, strip, flow, morsels and shapes	<ul style="list-style-type: none"> • Osteoconduction • Bioresorbable • Osteoinduction 	<ul style="list-style-type: none"> • Human studies • Case reports • Animal studies 	• 510(k) cleared
Osteotech	Grafton®	DBM combined with Glycerol	Formable putty, injectable gel, putty mixed with chips, flexible sheets and matrix	<ul style="list-style-type: none"> • Osteoconduction • Bioresorbable • Osteoinduction 	<ul style="list-style-type: none"> • Published human studies • Case reports • Animal studies 	• 510(k) cleared
	Grafton Plus®	DBM combined with a starch carrier	Paste	<ul style="list-style-type: none"> • Osteoconduction • Bioresorbable • Osteoinduction 	<ul style="list-style-type: none"> • Case reports • Animal studies 	• 510(k) cleared
Regeneration Technologies	BioSet™	DBM combined with natural gelatin carrier	Injectable paste, injectable putty, strips and blocks with cortical cancellous chips	<ul style="list-style-type: none"> • Osteoconduction • Bioresorbable • Osteoinduction 	<ul style="list-style-type: none"> • Human studies • Case reports • Animal studies • Every lot tested <i>in vivo</i> for osteoinduction 	• 510(k) cleared
Smith & Nephew	VIAGRAF	DBM combined with glycerol	Putty, paste, gel, crunch and flex	<ul style="list-style-type: none"> • Osteoconduction • Bioresorbable • Osteoinduction 	<ul style="list-style-type: none"> • Animal studies 	• 510(k) cleared
Stryker Biotech	OP-1® Implant	rhBMP-7 with type 1 bone collagen	Lyophilized powder reconstituted to form wet sand	<ul style="list-style-type: none"> • Bioresorbable scaffold • Osteoinduction 	<ul style="list-style-type: none"> • Human studies (Level I data) • Case reports • Animal studies 	• HDE approval for long bone nonunions
	OP-1® Putty	rhBMP-7 with type 1 bone collagen	Lyophilized powder reconstituted to form putty	<ul style="list-style-type: none"> • Bioresorbable scaffold • Osteoinduction 	<ul style="list-style-type: none"> • Human studies (Level I data) • Case reports • Animal studies 	• HDE approval for revision posterolateral fusion
	Calstrux®	Tricalcium phosphate with carboxymethylcellulose	Moldable putty	<ul style="list-style-type: none"> • Osteoconduction • Bioresorbable 	<ul style="list-style-type: none"> • Animal studies 	• 510(k) cleared
Synthes	Norian® SRS®	Calcium phosphate	Injectable paste	<ul style="list-style-type: none"> • Osteoconduction • Bioresorbable 	<ul style="list-style-type: none"> • Human studies • Case reports • Animal studies 	• 510(k) cleared
	Norian® SRS® Fast Set Putty	Calcium phosphate	Moldable putty	<ul style="list-style-type: none"> • Osteoconduction • Bioresorbable 	<ul style="list-style-type: none"> • Human studies • Case reports • Animal studies 	• 510(k) cleared
	chronOS®	β -tricalcium phosphate	Granules, blocks and wedges	<ul style="list-style-type: none"> • Osteoconduction • Bioresorbable 	<ul style="list-style-type: none"> • Animal studies 	• 510(k) cleared
	Calceon® 6	Calcium sulfate	Pellets	<ul style="list-style-type: none"> • Osteoconduction • Bioresorbable 	<ul style="list-style-type: none"> • Animal studies 	• 510(k) cleared

Company	Commercially available product	Composition	Commercially available forms	Claimed mechanisms of action	Burdens of proof	FDA status
Wright Medical Technology	OSTEOSET®	Surgical grade calcium sulfate	Various sized pellets	<ul style="list-style-type: none"> • Osteoconduction • Bioresorbable 	<ul style="list-style-type: none"> • Human studies • Case reports • Animal studies 	• 510(k) cleared
	MIIG® X3	High strength surgical grade calcium sulfate	Minimally invasive injectable graft for compression fractures	<ul style="list-style-type: none"> • Osteoconduction • Bioresorbable 	<ul style="list-style-type: none"> • Human studies • Case reports • Animal studies 	• 510(k) cleared
	CELLPLEX®	Tricalcium phosphate	Various sized granules	<ul style="list-style-type: none"> • Osteoconduction • Bioresorbable 	<ul style="list-style-type: none"> • Case reports • Animal studies 	• 510(k) cleared
	ALLOMATRIX®	DBM with/without CBM in surgical grade calcium sulfate powder	Various volumes of injectable/ formable putty	<ul style="list-style-type: none"> • Osteoconduction • Bioresorbable • Osteoinduction 	<ul style="list-style-type: none"> • Human studies • Case reports • Animal studies • Cell culture 	• 510(k) cleared
	ALLOMATRIX® RCS	DBM with CACIPLX™ Technology in surgical grade calcium sulfate powder	Various volumes of formable putty	<ul style="list-style-type: none"> • Osteoconduction • Bioresorbable • Osteoinduction 	<ul style="list-style-type: none"> • Animal studies 	• 510(k) cleared
	IGNITE®	DBM in surgical grade calcium sulfate powder to be mixed with bone marrow aspirate	Percutaneous graft for problem fractures	<ul style="list-style-type: none"> • Osteoconduction • Bioresorbable • Osteoinduction 	<ul style="list-style-type: none"> • Human studies • Case reports • Animal studies • Cell culture 	• 510(k) cleared
Zimmer	CopiOs®	Mixture of calcium phosphate, dibasic and type I collagen	Sponge	<ul style="list-style-type: none"> • Osteoconduction • Bioresorbable • Osteogenic and limited osteoinduction when combined with bone marrow aspirate 	<ul style="list-style-type: none"> • Animal studies 	• 510(k) cleared