

# THE EVOLVING ROLE OF BONE-GRAFT SUBSTITUTES

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## ORTHOPAEDIC DEVICE FORUM

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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)

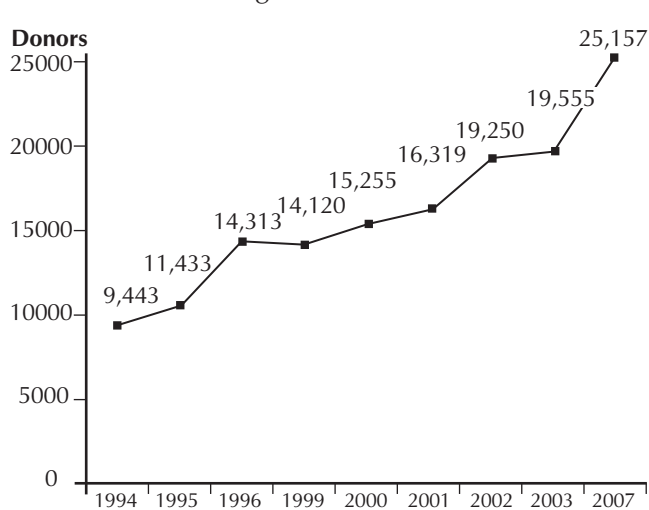


Figure 1: U.S. trends in musculoskeletal tissue donors. Source: AATB Annual Survey

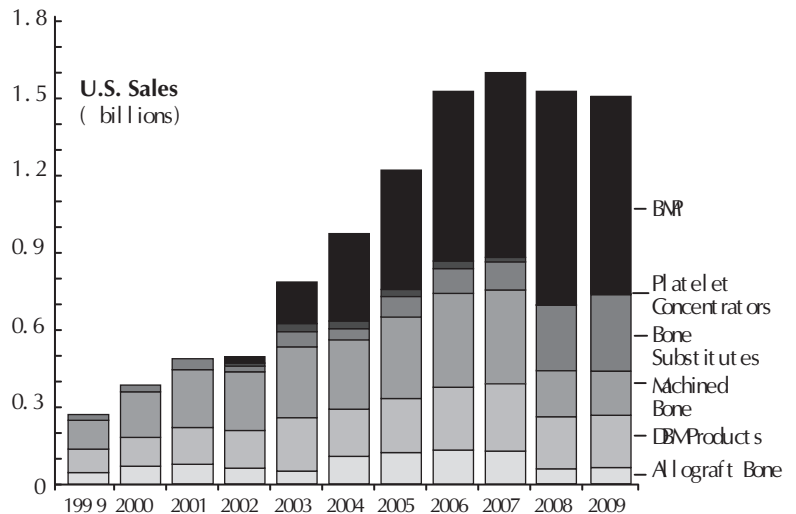


Figure 2: U.S. sales of bone graft and bone-graft substitutes Source: Orthopedic Network News

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-graft 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 inherently have all three properties in order to be clinically effective. When inductive molecules are locally delivered on a scaffold, mesenchymal stem cells are ultimately 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 equivalent or superiorly to autograft demonstrating efficacy as an autograft replacement.

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. However, the availability of autografts is 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 there is 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. Some tissue processors incorporate methods that may eliminate the risk. 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 inactivate viruses but 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

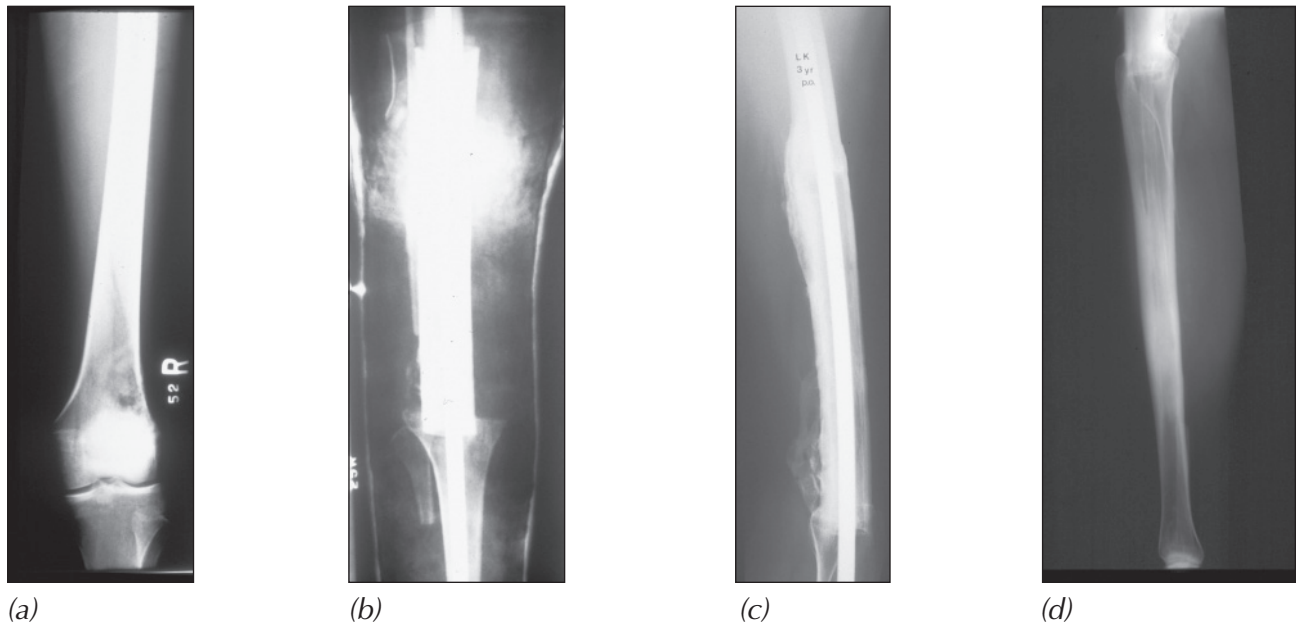


Figure 4: (a) A 17-year old patient with osteosarcoma of the distal femur with no extraosseous extension or metastatic disease. Following chemotherapy, (b) limb salvage with wide resection was performed. Femoral reconstruction with the use of an autogenous cortical fibular graft, iliac crest bone chips, 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 graft 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)

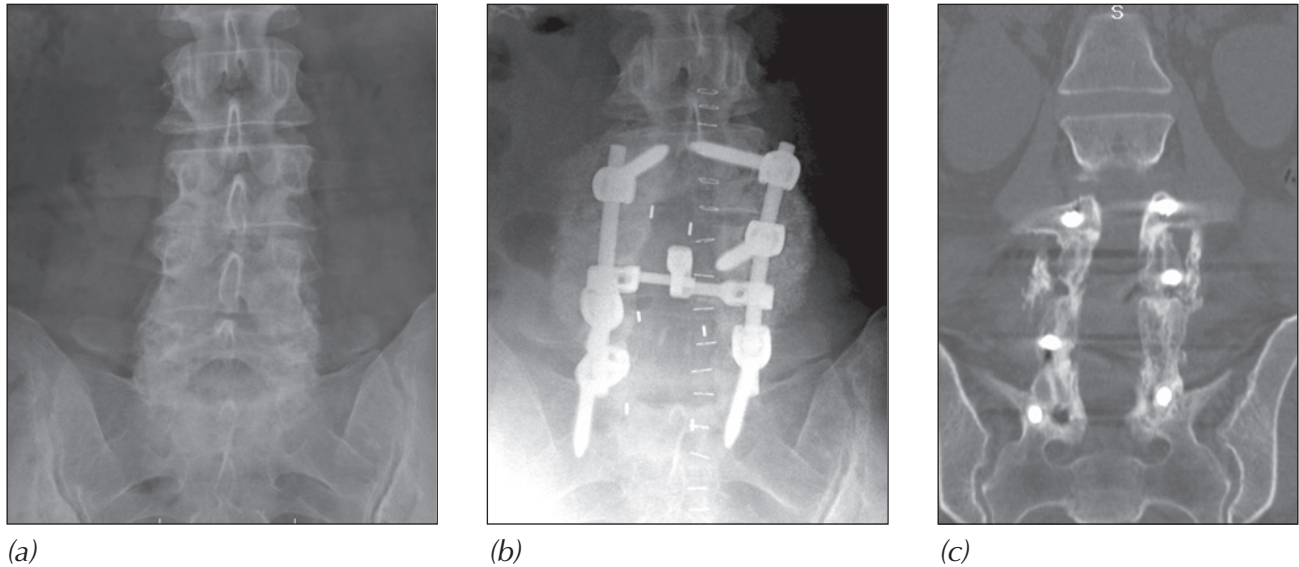


Figure 5: (a) A 65-year old female with a 1.5 year history of severe low back pain diagnosed with Grade I spondylolisthesis of the L4 on L5, bilateral neural foraminal stenosis and central stenosis impacting the L3-S1 levels. (b) X-ray after 1 month of treatment with Integra Mozaik™ Strip containing bone marrow aspirate (BMA) on the left posterolateral gutter and autograft on the right side. (c) CT scan after 17 months postoperative shows bilateral fusion across the three levels.

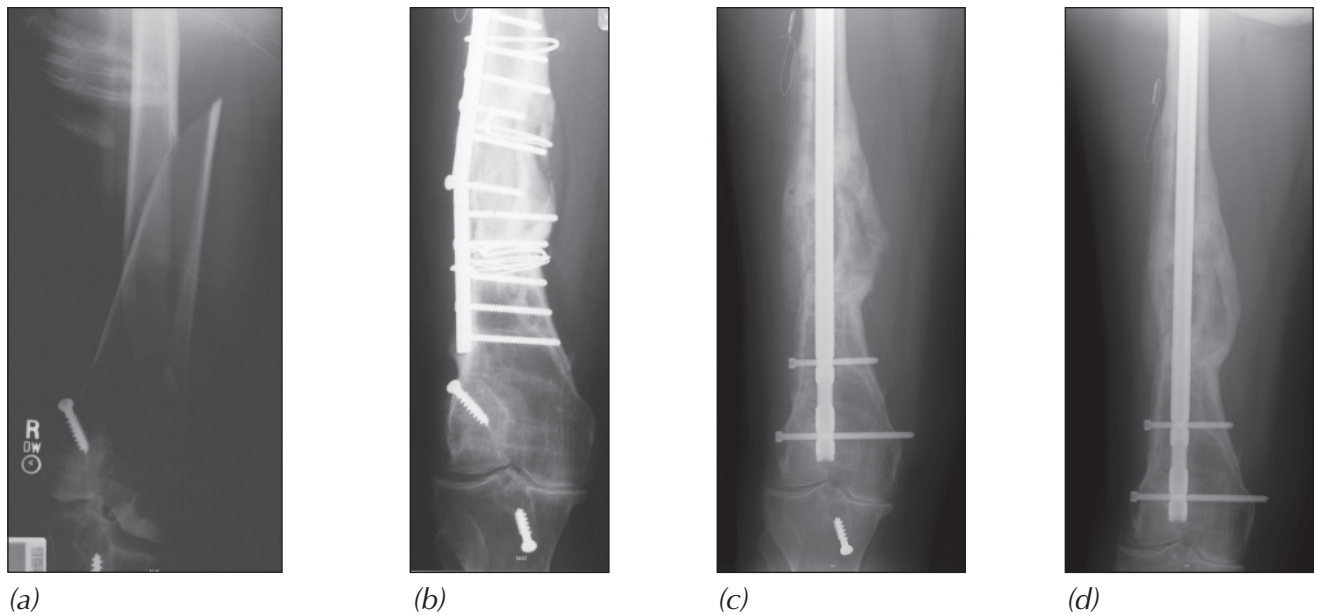


Figure 6: (a) A 58-year old obese female with a nonunion of the right femur after falling from a horse. Treatments included plating with cortical struts and DBM. (b) Nine months following third surgery the plate and several screws are broken. (c) Three months after treatment with IM rod fixation and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

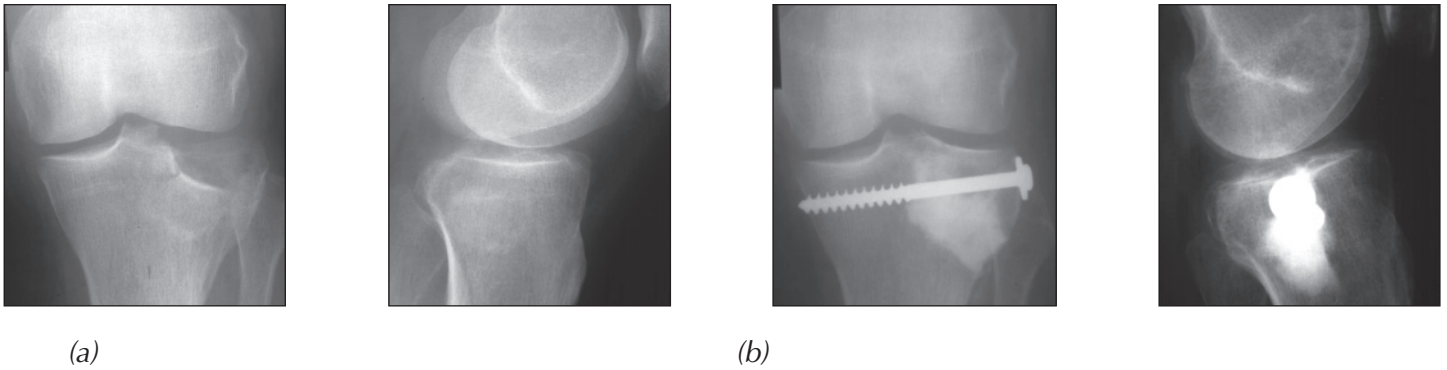


Figure 7: (a) AP and Lateral radiographs, 67-year old female with depressed fracture of the lateral tibial plateau. (b) AP and Lateral radiographs 12 months after ORIF with filling the defect with Norian® SRS® (Synthes USA, Paoli, PA). No loss of reduction of the plateau surface is noted, fracture completely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

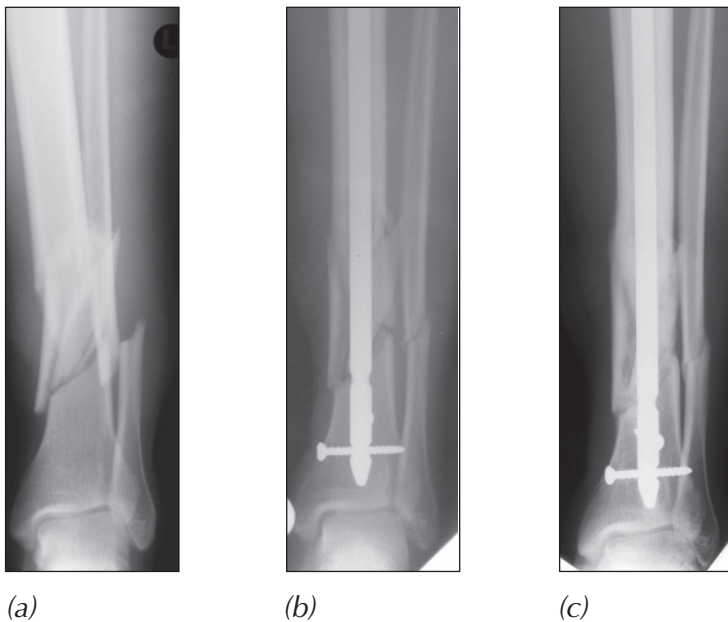


Figure 8: (a) A 29-year old male with a Grade III B oblique fracture of the distal tibia from a motorcycle accident. (b) Six weeks after being treated with an unreamed locked nail and INFUSE® Bone Graft (Medtronic Spinal & Biologics, Memphis, TN). (c) Patient full weight bearing and radiographically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

## BURDEN OF PROOF

It is reasonable to assume that not all bone-graft alternatives 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 alternative 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 clinical and preclinical studies to justify the use of an osteoinductive graft material or the choice of one alternative over another. It is generally more difficult to make bone in humans than it is in larger order animals. 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.)



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## 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. When DBM products include additives, they 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 regulatory requirements, testing in relevant animal models is limited or absent and there is a risk that they will not produce the expected results in humans.

## 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 Humanitarian Use Device (HDE) approved as an alternative to autograft in recalcitrant long bone nonunions where the use of autograft is unfeasible and alternative treatments have failed; 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 harvest 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-graft 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. 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-graft 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 bone repair 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 - 2010

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"> <li>Osteoconduction</li> <li>Bioresorbable</li> <li>Osteoinduction</li> </ul>	<ul style="list-style-type: none"> <li>Case reports</li> <li>Animal studies</li> <li>Cell culture</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Graft Extender</li> <li>Bone Void Filler</li> </ul>
Biomet Osteobiologics	BonePlast®	Calcium sulfate with or without HA/CC composite granules	Various volumes of powder and setting solution	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> </ul>	<ul style="list-style-type: none"> <li>Case reports</li> <li>Animal studies</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Void Filler</li> </ul>
	BonePlast® Quick Set	Calcium sulfate	Quick setting paste	<ul style="list-style-type: none"> <li>Osteoconductive</li> <li>Bioresorbable</li> </ul>	<ul style="list-style-type: none"> <li>Case reports</li> <li>Animal studies</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Void Filler</li> </ul>
	InterGro®	DBM in a lecithin carrier	Paste, putty and mix with HA/CC composite granules	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> <li>Osteoinduction</li> </ul>	<ul style="list-style-type: none"> <li>Case reports</li> <li>Animal studies</li> <li>Every lot tested for osteoinduction</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Graft Extender</li> <li>Bone Void Filler</li> </ul>
	ProOsteon® 500R	Coralline-derived HA/CC composite	Granular or block	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> </ul>	<ul style="list-style-type: none"> <li>Human studies</li> <li>Case reports</li> <li>Animal studies</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Void Filler</li> </ul>
DePuy Spine	CONDUIT® TCP Granules	100% β-TCP	Granules	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> </ul>	<ul style="list-style-type: none"> <li>Case reports</li> <li>Animal studies</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Void Filler</li> </ul>
	HEALOS® Bone Graft Replacement	Mineralized collagen matrix	Variety of strip sizes	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Creeping substitution</li> <li>Osteoinduction</li> <li>Osteogenesis when mixed with bone marrow aspirate</li> </ul>	<ul style="list-style-type: none"> <li>Peer-reviewed, published human studies</li> <li>Case reports</li> <li>Animal studies</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Void Filler: Must be used with autogenous bone marrow</li> </ul>
Exactech	Optecure®	DBM suspended in a hydrogel carrier	Dry mix kit delivered with buffered saline	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> <li>Osteoinduction</li> <li>Osteogenesis when mixed with autogenous bone graft</li> </ul>	<ul style="list-style-type: none"> <li>Human studies</li> <li>Case reports</li> <li>Animal studies</li> <li>Every lot tested <i>in vivo</i> for osteoinduction</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Graft Extender</li> <li>Bone Void Filler</li> </ul>
	Optecure® + CCC	DBM and CCC suspended in a hydrogel carrier	Dry mix kit delivered with buffered saline	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> <li>Osteoinduction</li> <li>Osteogenesis when mixed with autogenous bone graft</li> </ul>	<ul style="list-style-type: none"> <li>Human studies</li> <li>Case reports</li> <li>Animal studies</li> <li>Every lot tested <i>in vivo</i> for osteoinduction</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Graft Extender</li> <li>Bone Void Filler</li> </ul>
	Optefil®	DBM suspended in gelatin carrier	Injectable bone paste-dry powder ready to be hydrated	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> <li>Osteoinduction</li> <li>Osteogenesis when mixed with autogenous bone graft</li> </ul>	<ul style="list-style-type: none"> <li>Human studies</li> <li>Case reports</li> <li>Animal studies</li> <li>Every lot tested <i>in vivo</i> for osteoinduction</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Void Filler</li> </ul>
	Opteform®	DBM and cortical cancellous chips suspended in gelatin carrier	Formable putty or dry powder ready to be hydrated	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> <li>Osteoinduction</li> <li>Osteogenesis when mixed with autogenous bone graft</li> </ul>	<ul style="list-style-type: none"> <li>Human studies</li> <li>Case reports</li> <li>Animal studies</li> <li>Every lot tested <i>in vivo</i> for osteoinduction</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Void Filler</li> </ul>
	OpteMx™	HA/TCP biphasic combination	Granules, sticks, rounded wedges, wedges and cylinders in several sizes	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> <li>Compressive strength of 400psi</li> <li>Osteogenesis and limited osteoinduction when mixed with bone marrow aspirate</li> </ul>	<ul style="list-style-type: none"> <li>Human studies</li> <li>Case reports</li> <li>Animal studies</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Void Filler</li> </ul>

β-TCP - β-tricalcium phosphate  
CBM - Cancellous bone matrix

CCC - Cortical cancellous chips  
DBM - Demineralized bone matrix

HA/CC - Hydroxyapatite/calcium carbonate

PMA – Pre-Market Application; HDE – Humanitarian Device Exemption

Company	Commercially available product	Composition	Commercially available forms	Claimed mechanisms of action	Burdens of proof	FDA status
Integra Orthobiologics/ (IsoTis Orthobiologics)	Accell Connexus®	DBM, Accell Bone Matrix, Reverse Phase Medium	Injectable putty	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> <li>Osteoinduction</li> </ul>	<ul style="list-style-type: none"> <li>Human studies</li> <li>Case reports</li> <li>Animal studies</li> <li>Every DBM lot tested for osteoinduction</li> </ul>	510(k) cleared Extremities, Pelvis • Bone Void Filler Extremities, Pelvis, Spine • Bone Graft Extender
	Accell Evo3™	DBM, Accell Bone Matrix, Reverse Phase Medium	Injectable putty	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> <li>Osteoinduction</li> </ul>	<ul style="list-style-type: none"> <li>Animal studies</li> <li>Every DBM lot tested for osteoinduction</li> </ul>	510(k) cleared Extremities, Pelvis • Bone Void Filler Extremities, Pelvis, Spine • Bone Graft Extender
	Accell TBM®	DBM, Accell Bone Matrix	Various sized strips	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> <li>Osteoinduction</li> </ul>	<ul style="list-style-type: none"> <li>Human studies</li> <li>Case reports</li> <li>Animal studies</li> <li>Every DBM lot tested for osteoinduction</li> </ul>	510(k) cleared Extremities, Pelvis • Bone Void Filler Extremities, Pelvis, Spine • Bone Graft Extender
	DynaGraft II	DBM, Reverse Phase Medium	Injectable putty	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> <li>Osteoinduction</li> </ul>	<ul style="list-style-type: none"> <li>Human studies</li> <li>Case reports</li> <li>Animal studies</li> <li>Every DBM lot tested for osteoinduction</li> </ul>	510(k) cleared
	OrthoBlast II	DBM, cancellous bone, Reverse Phase Medium	Injectable putty	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> <li>Osteoinduction</li> </ul>	<ul style="list-style-type: none"> <li>Human studies</li> <li>Case reports</li> <li>Animal studies</li> <li>Every DBM lot tested for osteoinduction</li> </ul>	510(k) cleared Extremities, Pelvis • Bone Void Filler Extremities, Pelvis, Spine • Bone Graft Extender
	Integra Mozaik™	80% highly purified $\beta$ -TCP/ 20% highly purified Type-1 collagen	Strip and putty	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> </ul>	<ul style="list-style-type: none"> <li>Human studies</li> <li>Case reports</li> <li>Animal studies</li> </ul>	510(k) cleared Extremities, Pelvis, Spine • Bone Void Filler
Life Net Health	IC Graft Chamber®	DBM particles and cancellous chips	Lyophilized and packaged in various sizes within a delivery chamber	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> <li>Osteoinduction</li> <li>Designed to be used with blood, PRP or bone marrow to enhance DBM activity</li> </ul>	<ul style="list-style-type: none"> <li>Animal studies</li> <li>Case reports</li> </ul>	• Regulated under CFR 1270 and 1271 as a human tissue and 510(k) cleared
	Optium DBM®	DBM combined with glycerol carrier	Formable putty (bone fibers) and injectable gel (bone particles)	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> <li>Osteoinduction</li> </ul>	<ul style="list-style-type: none"> <li>Human studies</li> <li>Case reports</li> <li>Animal studies</li> </ul>	510(k) cleared • Bone Void Filler
Medtronic Spinal & Biologics	INFUSE® Bone Graft	rhBMP-2 protein on an absorbable collagen sponge	Multiple kit sizes	<ul style="list-style-type: none"> <li>Bioresorbable carrier</li> <li>Osteoinduction</li> <li>Chemotaxis of stem cells; indirect osteogenesis</li> </ul>	<ul style="list-style-type: none"> <li>Human studies (Level I and Level III data)</li> <li>Case reports</li> <li>Animal studies</li> </ul>	• PMA approved for fusion with spinal cage • PMA approved for open tibia fractures with IM nail
	MasterGraft® Granules	Biphasic calcium phosphate (15% HA / 85% $\beta$ -TCP)	Granules	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> </ul>	<ul style="list-style-type: none"> <li>Animal studies</li> <li>Case reports</li> </ul>	510(k) cleared • Bone Void Filler
	MasterGraft® Matrix	Biphasic calcium phosphate and collagen	Compression resistant block	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> </ul>	<ul style="list-style-type: none"> <li>Animal studies</li> <li>Case reports</li> </ul>	510(k) cleared • Bone Void Filler: Must be used with autogenous bone marrow

$\beta$ -TCP -  $\beta$ -tricalcium phosphate  
CBM - Cancellous bone matrix

CCC - Cortical cancellous chips  
DBM - Demineralized bone matrix

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PMA – Pre-Market Application; HDE – Humanitarian Device Exemption



Company	Commercially available product	Composition	Commercially available forms	Claimed mechanisms of action	Burdens of proof	FDA status
Medtronic Spinal & Biologics	MasterGraft® Putty	Biphasic calcium phosphate and collagen	Moldable putty	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> </ul>	<ul style="list-style-type: none"> <li>Animal studies</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Graft Extender: Must be used with autograft</li> <li>Bone Void Filler: Must be used with autogenous bone marrow and/or autograft and/or sterile water</li> </ul>
	MasterGraft® Strip	Biphasic calcium phosphate (15% HA and 85% $\beta$ -TCP) and collagen	Compression resistant strip	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> </ul>	<ul style="list-style-type: none"> <li>Animal studies</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Void Filler: Must be used with autogenous bone marrow</li> </ul>
	Osteofil® DBM	DBM in porcine gelatin	Injectable paste and moldable strips	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> <li>Osteoinduction</li> </ul>	<ul style="list-style-type: none"> <li>Animal studies</li> <li>Case reports</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Void Filler</li> </ul>
	Progenix™ Plus	DBM in Type-1 bovine collagen and sodium alginate	Putty with demineralized cortical bone chips	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> <li>Osteoinduction</li> </ul>	<ul style="list-style-type: none"> <li>Animal studies</li> <li>Case reports</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Graft Substitute</li> <li>Bone Graft Extender</li> <li>Bone Void Filler</li> </ul>
	Progenix™ Putty	DBM in Type-1 bovine collagen and sodium alginate	Ready to use injectable putty	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> <li>Osteoinduction</li> </ul>	<ul style="list-style-type: none"> <li>Animal studies</li> <li>Case reports</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Extremities, Pelvis</li> <li>Bone Graft Substitute</li> <li>Bone Void Filler</li> <li>Spine</li> <li>Bone Graft Extender: Must be used with autograft bone</li> </ul>
MTF/Orthofix	Trinity Evolution™	Viable Cellular Bone Matrix	Multiple volumes available	<ul style="list-style-type: none"> <li>Osteogenesis</li> <li>Osteoinduction</li> <li>Osteoconduction</li> </ul>	<ul style="list-style-type: none"> <li>Animal Studies</li> <li>Case Reports</li> </ul>	<ul style="list-style-type: none"> <li>Regulated under CFR 1270 and 1271 as a human tissue.</li> </ul>
MTF/Synthes	DBX®	DBM in sodium hyaluronate carrier	Paste, putty mix and strip	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> <li>Osteoinduction</li> </ul>	<ul style="list-style-type: none"> <li>Human studies</li> <li>Case reports</li> <li>Animal studies</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Graft Extender</li> <li>Bone Void Filler</li> </ul>
NovaBone/MTF	NovaBone®	Bioactive silicate	Particulate, putty and morsels	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> <li>Osteostimulation</li> </ul>	<ul style="list-style-type: none"> <li>Published human studies</li> <li>Case reports</li> <li>Animal studies</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Void Filler</li> </ul>
Orthovita	Vitoss®	100% $\beta$ -TCP and 80% $\beta$ -TCP/20% collagen and 70% $\beta$ -TCP/20% collagen/10% bioactive glass	Putty, strip, flow, morsels and shapes	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> <li>Bioactive/osteostimulation</li> <li>Osteogenesis and osteoinduction when mixed with bone marrow aspirate</li> </ul>	<ul style="list-style-type: none"> <li>Published human studies (Level I and III)</li> <li>Case reports</li> <li>Animal studies</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Void Filler</li> </ul>

$\beta$ -TCP -  $\beta$ -tricalcium phosphate      CCC - Cortical cancellous chips      HA/CC - Hydroxyapatite/calcium carbonate  
CBM - Cancellous bone matrix      DBM - Demineralized bone matrix  
PMA – Pre-Market Application; HDE – Humanitarian Device Exemption

Company	Commercially available product	Composition	Commercially available forms	Claimed mechanisms of action	Burdens of proof	FDA status
Osteotech	GRAFTON® A-Flex®	DBM fiber technology	Round flexible sheet	<ul style="list-style-type: none"> <li>Osteoinduction</li> <li>Osteoconduction</li> <li>Incorporation/ complete remodelling</li> <li>Osteogenesis when mixed with bone marrow aspirate or autogenous bone graft</li> </ul>	<ul style="list-style-type: none"> <li>Peer-reviewed published human studies (incl. Level I-II prospective studies)</li> <li>Case Reports</li> <li>Animal Studies</li> <li>Every lot tested <i>in vivo</i> for osteoinduction</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Graft Substitute</li> <li>Bone Graft Extender</li> <li>Bone Void Filler</li> </ul>
	GRAFTON® Crunch®	DBM fibers with demineralized cortical cubes	Packable graft	<ul style="list-style-type: none"> <li>Osteoinduction</li> <li>Osteoconduction</li> <li>Incorporation/ complete remodelling</li> <li>Osteogenesis when mixed with bone marrow aspirate or autogenous bone graft</li> </ul>	<ul style="list-style-type: none"> <li>Peer-reviewed published human studies (incl. Level I-II prospective studies)</li> <li>Case reports</li> <li>Animal studies</li> <li>Every lot tested <i>in vivo</i> for osteoinduction</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Graft Substitute</li> <li>Bone Graft Extender</li> <li>Bone Void Filler</li> </ul>
	GRAFTON® Flex®	DBM fiber technology	Various sizes of flexible sheets	<ul style="list-style-type: none"> <li>Osteoinduction</li> <li>Osteoconduction</li> <li>Incorporation/ complete remodelling</li> <li>Osteogenesis when mixed with bone marrow aspirate or autogenous bone graft</li> </ul>	<ul style="list-style-type: none"> <li>Peer-reviewed published human studies (incl. Level I-II prospective studies)</li> <li>Case reports</li> <li>Animal studies</li> <li>Every lot tested <i>in vivo</i> for osteoinduction</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Graft Substitute</li> <li>Bone Graft Extender</li> <li>Bone Void Filler</li> </ul>
	GRAFTON® Gel	DBM in a syringe	MIS and Percutaneous injectable graft	<ul style="list-style-type: none"> <li>Osteoinduction</li> <li>Osteoconduction</li> <li>Incorporation/ complete remodelling</li> <li>Osteogenesis when mixed with bone marrow aspirate or autogenous bone graft</li> </ul>	<ul style="list-style-type: none"> <li>Peer-reviewed published human studies (incl. Level I-II prospective studies)</li> <li>Case reports</li> <li>Animal studies</li> <li>Every lot tested <i>in vivo</i> for osteoinduction</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Graft Substitute</li> <li>Bone Graft Extender</li> <li>Bone Void Filler</li> </ul>
	GRAFTON® Matrix PLF	DBM fiber technology	Single and double troughs	<ul style="list-style-type: none"> <li>Osteoinduction</li> <li>Osteoconduction</li> <li>Incorporation/ complete remodelling</li> <li>Osteogenesis when mixed with bone marrow aspirate or autogenous bone graft</li> </ul>	<ul style="list-style-type: none"> <li>Peer-reviewed published human studies (incl. Level I-II prospective studies)</li> <li>Case reports</li> <li>Animal studies</li> <li>Every lot tested <i>in vivo</i> for osteoinduction</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Graft Substitute</li> <li>Bone Graft Extender</li> <li>Bone Void Filler</li> </ul>
	GRAFTON® Matrix Scoliosis Strips	DBM fiber technology	Various sizes of strips	<ul style="list-style-type: none"> <li>Osteoinduction</li> <li>Osteoconduction</li> <li>Incorporation/ complete remodelling</li> <li>Osteogenesis when mixed with bone marrow aspirate or autogenous bone graft</li> </ul>	<ul style="list-style-type: none"> <li>Peer-reviewed published human studies (incl. Level I-II prospective studies)</li> <li>Case reports</li> <li>Animal studies</li> <li>Every lot tested <i>in vivo</i> for osteoinduction</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Graft Substitute</li> <li>Bone Graft Extender</li> <li>Bone Void Filler</li> </ul>
	GRAFTON® Orthoblend Large Defect	DBM fibers with crushed cancellous chips	Packable graft	<ul style="list-style-type: none"> <li>Osteoinduction</li> <li>Osteoconduction</li> <li>Incorporation/ complete remodelling</li> <li>Osteogenesis when mixed with bone marrow aspirate or autogenous bone graft</li> </ul>	<ul style="list-style-type: none"> <li>Peer-reviewed published human studies (incl. Level I-II prospective studies)</li> <li>Case reports</li> <li>Animal studies</li> <li>Every lot tested <i>in vivo</i> for osteoinduction</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Graft Substitute</li> <li>Bone Graft Extender</li> <li>Bone Void Filler</li> </ul>
	GRAFTON® Orthoblend Small Defect	DBM fibers with larger cancellous chips	Packable moldable graft	<ul style="list-style-type: none"> <li>Osteoinduction</li> <li>Osteoconduction</li> <li>Incorporation/ complete remodelling</li> <li>Osteogenesis when mixed with bone marrow aspirate or autogenous bone graft</li> </ul>	<ul style="list-style-type: none"> <li>Peer-reviewed published human studies (incl. Level I-II prospective studies)</li> <li>Case reports</li> <li>Animal studies</li> <li>Every lot tested <i>in vivo</i> for osteoinduction</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Graft Substitute</li> <li>Bone Graft Extender</li> <li>Bone Void Filler</li> </ul>

β-TCP - β-tricalcium phosphate  
CBM - Cancellous bone matrix

CCC - Cortical cancellous chips  
DBM - Demineralized bone matrix

HA/CC - Hydroxyapatite/calcium carbonate

PMA – Pre-Market Application; HDE – Humanitarian Device Exemption

Company	Commercially available product	Composition	Commercially available forms	Claimed mechanisms of action	Burdens of proof	FDA status
Osteotech	GRAFTON Plus® Paste	DBM in a syringe	Injectable MIS graft, resists irrigation	<ul style="list-style-type: none"> <li>Osteoinduction</li> <li>Osteoconduction</li> <li>Incorporation/ complete remodelling</li> <li>Osteogenesis when mixed with bone marrow aspirate or autogenous bone graft</li> </ul>	<ul style="list-style-type: none"> <li>Peer-reviewed published human studies (incl. Level I-II prospective studies)</li> <li>Case reports</li> <li>Animal studies</li> <li>Every lot tested <i>in vivo</i> for osteoinduction</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Graft Substitute</li> <li>Bone Graft Extender</li> <li>Bone Void Filler</li> </ul>
	GRAFTON® Putty	DBM fiber technology	Packable moldable graft	<ul style="list-style-type: none"> <li>Osteoinduction</li> <li>Osteoconduction</li> <li>Incorporation/ complete remodelling</li> <li>Osteogenesis when mixed with bone marrow aspirate or autogenous bone graft</li> </ul>	<ul style="list-style-type: none"> <li>Peer-reviewed published human studies (incl. Level I-II prospective studies)</li> <li>Case reports</li> <li>Animal studies</li> <li>Every lot tested <i>in vivo</i> for osteoinduction</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Graft Substitute</li> <li>Bone Graft Extender</li> <li>Bone Void Filler</li> </ul>
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"> <li>Osteoconduction</li> <li>Bioresorbable</li> <li>Osteoinduction</li> </ul>	<ul style="list-style-type: none"> <li>Human studies</li> <li>Case reports</li> <li>Animal studies</li> <li>Every lot tested <i>in vivo</i> for osteoinduction</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Void Filler</li> </ul>
Smith & Nephew	VIAGRAF	DBM combined with glycerol	Putty, paste, gel, crunch and flex	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> <li>Osteoinduction</li> </ul>	<ul style="list-style-type: none"> <li>Animal studies</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Void Filler</li> </ul>
Stryker Biotech	OP-1® Implant	rhBMP-7 with Type-1 bone collagen	Lyophilized powder reconstituted with saline to form wet sand-like consistency	<ul style="list-style-type: none"> <li>Bioresorbable scaffold</li> <li>Osteoinduction</li> </ul>	<ul style="list-style-type: none"> <li>Human studies (Level I data)</li> <li>Case reports</li> <li>Animal studies</li> </ul>	<ul style="list-style-type: none"> <li>HDE approval for long bone nonunions</li> </ul>
	OP-1® Putty	rhBMP-7 with Type-1 bone collagen plus carboxymethyl-cellulose (putty additive)	Lyophilized powder reconstituted with saline to form wet sand-like consistency	<ul style="list-style-type: none"> <li>Bioresorbable scaffold</li> <li>Osteoinduction</li> </ul>	<ul style="list-style-type: none"> <li>Human studies (Level I data)</li> <li>Case reports</li> <li>Animal studies</li> </ul>	<ul style="list-style-type: none"> <li>HDE approval for revision posterolateral lumbar fusion</li> </ul>
Synthes	Calceon® 6	Calcium sulfate	Pellets	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> </ul>	<ul style="list-style-type: none"> <li>Animal studies</li> </ul>	510(k) cleared
	chronOS®	β-TCP	Granules, blocks and wedges	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> </ul>	<ul style="list-style-type: none"> <li>Animal studies</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Void Filler</li> </ul>
	Norian® SRS®	Calcium phosphate	Injectable paste	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> </ul>	<ul style="list-style-type: none"> <li>Human studies</li> <li>Case reports</li> <li>Animal studies</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Void Filler</li> </ul>
	Norian® SRS® Fast Set Putty	Calcium phosphate	Moldable putty	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> </ul>	<ul style="list-style-type: none"> <li>Human studies</li> <li>Case reports</li> <li>Animal studies</li> </ul>	510(k) cleared <ul style="list-style-type: none"> <li>Bone Void Filler</li> </ul>

β-TCP - β-tricalcium phosphate  
 CBM - Cancellous bone matrix

CCC - Cortical cancellous chips  
 DBM - Demineralized bone matrix

HA/CC - Hydroxyapatite/calcium carbonate

PMA – Pre-Market Application; HDE – Humanitarian Device Exemption

Company	Commercially available product	Composition	Commercially available forms	Claimed mechanisms of action	Burdens of proof	FDA status
Wright Medical Technology	ALLOMATRIX®	DBM with/without CBM in surgical grade calcium sulfate powder	Various volumes of injectable/ formable putty	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> <li>Osteoinduction</li> </ul>	<ul style="list-style-type: none"> <li>Human studies</li> <li>Case reports</li> <li>Animal studies</li> <li>Cell culture</li> </ul>	510(k) cleared • Bone Void Filler
	ALLOMATRIX® RCS	DBM with CACIPLEX™ technology in surgical grade calcium sulfate powder	Various volumes of formable putty	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> <li>Osteoinduction</li> </ul>	<ul style="list-style-type: none"> <li>Animal studies</li> </ul>	510(k) cleared • Bone Void Filler
	ALLOPURE™	Sterile femoral/tibial allograft	12mm Evans wedge 6mm Cotton wedge	<ul style="list-style-type: none"> <li>Osteoconduction</li> </ul>	<ul style="list-style-type: none"> <li>Mechanical Testing</li> </ul>	<ul style="list-style-type: none"> <li>100% derived from allograft tissue</li> <li>Regulated under 21 CFR Parts 1270 and 1271 as a human tissue</li> </ul>
	CANCELLO-PURE® Wedges	Bovine bone	10mm x 50mm wedge 12mm Evans wedge 6mm Cotton wedge	<ul style="list-style-type: none"> <li>Osteoconduction</li> </ul>	<ul style="list-style-type: none"> <li>Case reports</li> <li>Animal studies</li> </ul>	510(k) cleared • Bone Void Filler
	CELLPLEX®	β-TCP	Various sized granules	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> </ul>	<ul style="list-style-type: none"> <li>Case reports</li> <li>Animal studies</li> </ul>	510(k) cleared • Bone Void Filler
	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"> <li>Osteoconduction</li> <li>Bioresorbable</li> <li>Osteoinduction</li> </ul>	<ul style="list-style-type: none"> <li>Human studies</li> <li>Case reports</li> <li>Animal studies</li> <li>Cell culture</li> </ul>	510(k) cleared • Bone Void Filler
	MIIG® X3	High strength surgical grade calcium sulfate	Minimally invasive injectable graft for compression fractures	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> </ul>	<ul style="list-style-type: none"> <li>Human studies</li> <li>Case reports</li> <li>Animal studies</li> </ul>	510(k) cleared • Bone Void Filler
	OSTEOSET®	Surgical grade calcium sulfate	Various sized pellets	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> </ul>	<ul style="list-style-type: none"> <li>Human studies</li> <li>Case reports</li> <li>Animal studies</li> </ul>	510(k) cleared • Bone Void Filler
	PRO-DENSE® Injectable Regenerative Graft	75% calcium sulfate and 25% calcium phosphate	Procedure kits, various volumes of injectable paste	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> <li>Dense bone regeneration</li> </ul>	<ul style="list-style-type: none"> <li>Human studies</li> <li>Case reports</li> <li>Animal studies</li> </ul>	510(k) cleared • Bone Void Filler
	PRO-STIM™ Injectable Inductive Graft	50% calcium sulfate, 10% calcium phosphate, and 40% DBM by weight	Procedure kits, various volumes of injectable paste/ formable putty	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> <li>Osteoinduction</li> </ul>	<ul style="list-style-type: none"> <li>Case reports</li> <li>Animal studies</li> </ul>	510(k) cleared • Resorbable calcium salt bone void filler device
Zimmer	CopiOs® Bone Void Filler	Dibasic calcium phosphate and Type-1 collagen	Sponge and paste	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Accelerated healing vs. autograft</li> <li>Bioresorbable</li> <li>Osteogenesis and osteoinduction when mixed with bone marrow aspirate</li> </ul>	<ul style="list-style-type: none"> <li>Case reports</li> <li>Animal studies</li> </ul>	510(k) cleared • Bone Void Filler: Must be used with autologous blood products like blood or bone marrow
	CopiOs® Cancellous Bone Graft	Bovine bone	Cancellous chips, cancellous cubes and cortico-cancellous wedges	<ul style="list-style-type: none"> <li>Osteoconduction</li> </ul>	<ul style="list-style-type: none"> <li>Case reports</li> <li>Animal studies</li> </ul>	510(k) cleared • Bone Void Filler
	Puros® DBM	Allograft DBM putty (putty with chips includes allograft chips from the same donor)	Putty and putty with chips	<ul style="list-style-type: none"> <li>Osteoconduction</li> <li>Bioresorbable</li> <li>Osteoinduction</li> </ul>	<ul style="list-style-type: none"> <li>Every lot tested in an <i>in vivo</i> rat assay for osteoinductive potential demonstrating bone formation in an ectopic model</li> </ul>	<ul style="list-style-type: none"> <li>100% derived from allograft tissue</li> <li>Regulated under 21 CFR Parts 1270 and 1271 as a human tissue</li> </ul>

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