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Review Article

# Review of commercially available demineralized bone matrix products for spinal fusions: A selection paradigm

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## Abstract

**Background:** Spinal fusions are commonly performed in the US each year for various spinal pathologies. There are multiple commercially available graft material options for these procedures, including an abundance of demineralized bone matrix (DBM) products.

**Methods:** This study reviews, clearly organizes, and puts forth meaningful information on select biological and physical properties of several commercially available DBM products. In addition, we provide an alternative classification method of DBM products by carrier.

**Results:** This review takes a closer look at the commercial and distributor practices of these products and companies in order to increase transparency between the consumer and source companies.

**Conclusions:** We propose a novel patient-centered approach to DBM product selection. This requires prioritizing patient safety, product effectiveness, and product transparency. This review offers a practical paradigm to facilitate informed product choice for surgeons and hospital systems alike.

**Key Words:** Allograft bone, demineralized bone matrix, DBM, iliac crest bone graft

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## INTRODUCTION

Between 1998 and 2008, the annual number of spinal fusion discharges in the United States increased 137%, causing a 7.9-fold increase in the national bill for spinal fusion.[10] This amounts to $40 billion – the largest national bill of any hospital-based surgery.[7]

Iliac crest bone graft (ICBG) has been the historical "gold-standard" source of autograft material used to promote spinal fusion. The advantages of ICBG and other local autografts are their osteoinductive (OI), osteoconductive, and osteogenic properties (e.g., no risk of rejection or disease transmission). Disadvantages include (1) a second surgical site, (2) graft site morbidity (often exaggerated), and (3) longer operation times. Furthermore, ICBG and other local autografts may not provide sufficient bone material for larger fusion areas, or there may be other host factors that contraindicate its use including active infection, tumor, or severe osteoporosis.



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Therefore, surgeons have long turned away from ICBG to allogeneic or synthetic sources of bone graft material, including freeze-dried allograft, fresh-frozen allograft, cancellous chips, ceramics, bone morphogenetic proteins (BMPs), demineralized bone matrix (DBM), and other permutations.[5]

The turn away from ICBG has facilitated the rise of many commercially available DBM products. There are few, if any, well-established algorithms or systematic approaches for surgeons and hospitals to decide which DBM products to utilize. This report discusses product safety, transparency and accurate labeling, biological properties, and physical properties while proposing a model paradigm that will facilitate effective DBM product selection.

## MATERIALS AND METHODS

### Ideal biological properties of demineralized bone matrix

The ideal DBM bone graft material (1) resists disease transmission or immune-mediated rejection, (2) incorporates completely into resident tissue, (3) promotes surface-level bone growth (termed osteoconductivity), (4) promotes bone-forming cells (osteoinductivity), and (5) fosters controlled osteogenesis, so as not to produce superfluous bone.[1]

### Ideal physical properties of demineralized bone matrix

A DBM graft material with ideal physical properties (1) increases total mass of the graft (graft extender), (2) serves as a scaffold with good mechanical strength, and (3) possesses favorable handling characteristics (e.g., pliability for manipulation into any size/shape to prevent migration).

### Harvesting and processing

There is significant variability in how DBM products are extracted, processed, and packaged. In general, DBM is typically extracted from cortical allograft bone, demineralized via acid extraction, sterilized, and combined with a carrier to prevent migration. Each DBM product has its advantages and disadvantages leading to variable fusion rates.[11] Furthermore, the variables in the processing/packaging of DBM can affect their successful clinical implementation.

### "White Boxing"

The term "white-boxing" is used describe the relative lack of information included with the different DBM products. Missing details include whether the product comes from a living or deceased donor, domestic or international source, and/or the bone composition of the product. While the Food and Drug Administration (FDA) uses the 510(k)* process to regulate some DBM products, unbiased reports of many are not routinely available.

### Variability of demineralized bone matrix products

Variability of DBM products has critical and lasting consequences for both clinicians and their patients. Here, we review the distributive methods, biological properties and quality control of several well-known DBM products in the interest of full disclosure and transparency. The authors synthesize and display information on "Distributor Company" and "Bone Content" of 33 DBM products. Note that distributor companies vary by region.

### Flyers

Materials on each product were obtained either through the source company's website or by contacting a company representative directly. Information not available in published documents are cited as personal communication or unpublished [Tables 1 and 2]. Here, we present a selection of some of the most commonly used DBM products.[4,9]

## RESULTS

### Summary of demineralized bone matrix products

There were 17 DBM products evaluated from ten source companies [Table 1]. The source companies were included to clarify the actual bone content and harvesting processes of these products to facilitate transparency. This table also includes information from each product's 510(k) summary statement regarding the FDA approved uses of the product.

DBM products come in a variety of forms, including sponges, strips, injectable putty, paste, and paste infused with chips. These various forms affect the products' ability to serve as graft extenders, enhancers, or substitutes.

### Demineralized bone matrix products organized by carrier

Thirty-three DBM products were organized by carrier substance [Table 2]. Twenty of these products contain a carrier and the remaining thirteen do not.

### Consideration of non-inflammatory properties of demineralized bone matrix

While the non-inflammatory qualities of DBM have been considered a beneficial characteristic of carriers, the precise role of inflammation in spinal fusion remains

*DBM is considered by the US FDA not to be a medical device, and it is categorized under the heading of human cells, tissues, and cellular and tissue-based products (HCT/P's). When DBM is combined with other components (sodium hyaluronate, glycerol, or calcium phosphate) intended to make DBM easier to handle by turning it into a putty or paste, it no longer qualifies for regulation solely as HCT/PS. They are regulated under the device provisions of the Federal Food, Drug, and Cosmetic Act. Thus, DBM can be regulated as either product depending on its composition.

**Table 1: Summary of DBM products and available information**

| Source company | DBM product | Distributor company | Carrier | Bone content | Available forms | FDA approved uses | OI Potential - lot tested |
|---|---|---|---|---|---|---|---|
| Allosource® | AlloFuse® | Allosource®* | Reverse phase medium | 36% DBM by weight (putty), 29% DBM by weight (gel) | Putty, gel, paste | Bone void filler, bone graft extender in extremities, pelvis, and spine | Each lot tested - *in vivo* |
| Bacterin International, Inc./XTANT Medical | OsteoSelect® | Bacterin* | Carboxymethylcellulose, phosphate-buffered saline | 74% DBM by dry weight | Putty | Bone void filler in extremities, pelvis, and posterolateral spine | Each lot tested - *in vivo* |
| | Osteosponge® | Bacterin* | No carrier | 100% DBM | Block, disc, SC, strip, filler | Non 510(k) regulated - nonmanipulated substance | |
| Lattice Biologics Ltd. | H-GENIN™ | Lattice Biologics Ltd. | No carrier | 100% DBM | Putty, crush-mix, spongeous blocks, powder | Non 510(k) regulated - nonmanipulated substance | Each lot tested - *in vivo** |
| Biomet/ Zimmer Biomet | InterGro® DBM | Biomet* | Lecithin | 40% DBM (putty), 35% DBM (paste), 35% (DBM plus) | Putty, paste, Plus mix with Pro Osteon 500R granules (hydroxyapatite over calcium carbonate core) | Bone void filler in extremities, pelvis, and spine, bone graft extender in spine | Each lot tested – *in vivo* |
| Integra™ Orthobiologics/ (IsoTis Orthobiologics) | Accell Connexus® | Varies by region* | Poloxamer reverse phase medium | 70% DBM by weight | Putty | Bone void filler in extremities and pelvis, bone graft extender in extremities, pelvis, and spine | Each lot tested – *in vitro* |
| | Accell Evo3™ | Varies by region* | Poloxamer reverse phase medium & cancellous bone chips | 70% DBM by weight | Putty | Bone void filler in extremities, pelvis, and posterolateral spine, bone graft extender in extremities, pelvis, and spine | Each lot tested – *in vitro* |
| | Accell TBM® | Varies by region* | No carrier | 100% DBM | Strip | Bone void filler in extremities and pelvis, bone graft extender in extremities, pelvis, and spine | Each lot tested – *in vitro* |
| | DynaGraft™ II | Varies by region* | Poloxamer reverse phase medium | Unpublished* | Putty, gel | Bone void filler in extremities and pelvis, bone graft extender in extremities, pelvis, and spine | Each lot tested - *in vitro* |
| | OrthoBlast™ II | Varies by region* | Poloxamer reverse phase medium & cancellous bone chips | Unpublished* | Putty, paste | Bone void filler in extremities and pelvis, bone graft extender in extremities, pelvis, and spine | Each lot tested - *in vitro* |

*Cont'd...*

**Table 1: Cont'd...**

| Source company | DBM product | Distributor company | Carrier | Bone content | Available forms | FDA approved uses | OI Potential - lot tested |
|---|---|---|---|---|---|---|---|
| LifeNet Health® | Optium® | LifeNet Health®* | Glycerol | Unpublished* | Putty, gel | Bone void filler in extremities, pelvis, and spine | Each lot tested - *in vivo* |
| Medtronic | Progenix Putty | SpinalGraft Technologies | Type-1 bovine collagen and sodium alginate | 70% | Putty | Bone void filler in extremities, pelvis, and spine | All lots tested |
| | DBX | MTF (Vendor)* | Sodium hyaluronate | 31% by weight (putty), 26% (paste), 35% (mix), 45% (strip) | Putty, paste, mix, strip | Bone void filler in extremity and pelvis | Each lot is tested using one or both of *in vivo* or *in vitro* |
| | GRAFTON® | Medtronic* | Unpublished | Unpublished | Gel, flex, putty, matrix, CRUNCH®, orthoblend, strips, paste | Bone void filler and bone graft extender in extremities, pelvis, and spine | Lot tested - *in vivo* |
| RTI Surgical®, Inc. | BioSet DBM | RTI Surgical®, Inc. | Porcine gelatin | 24% DBM by weight | Paste, strip, disc, with or without cancellous chips | Bone void filler in extremities, pelvis, and spine | Each lot tested |
| Wright™ Medical Technology | ALLOMATRIX® | Wright™ Medical Group | Surgical grade calcium sulfate | 86% by volume | Putty, provided in powder form | Bone void filler in extremities and pelvis, bone graft extender in spine | Each lot tested - *in vitro* |
| Zimmer | Puros® DBM | Varies by region* | No carrier | 100% DBM | Putty, putty with cortico-cancellous chips | Non 510(k) regulated – nonmanipulated substance | All lots tested - *in vivo* |

*Denotes personal communication with company representative

controversial. Inflammation plays a key role in recruiting osteoblasts to produce new bone, promote fusion, facilitate early healing, and encourage angiogenesis. Therefore, carriers with strong anti-inflammatory characteristics may not generate an optimal postoperative healing environment. On the other hand, excessive inflammation at the fusion site may lead to patient complications such as pain and stiffness. It is the surgeon-authors' opinion that some inflammation is useful to facilitate bone fusion.

### Impact of carriers for demineralized bone matrix products

Each carrier substance imparts its own unique properties onto its respective combined DBM product. Examples of commercially utilized carriers include calcium sulphate (Wright's Allomatrix®), sodium hyaluronate (Medtronic's DBX®), and porcine collagen (Medtronics' Osteofil®) [Table 2]. In the surgeon-author's opinion, none of these carriers are likely to harm patients in the amounts present; however, it is suspected that some carriers may be more beneficial than others. One might consider using a pure DBM without carrier to be more prudent until more research is done to identify the ideal carrier. In either case, improvement of product content awareness through transparent labeling of DBM will be beneficial.

### Similarity in demineralized bone matrix product nomenclature

White-boxed DBM products often share similar names leading to confusion. The names of the original bone source company, as well as the names of distributors and end products are strikingly similar, e.g., the AlloSource company produces AlloFuse® DBM, not to be confused with Wright Medical Technology's AlloMatrix® DBM [Table 1].

## DISCUSSION

The often confusing diversity of commercially available DBM products presents a problem to clinicians and hospital systems whose goal is to select the most efficient, cost-effective, and proven successful products for their patients. As mentioned before, variability of DBM products has important and lasting consequences for both clinician and patient. Of paramount importance in choosing a DBM product and successful clinical implementation are the following aspects:[2,3,12]

1. Donor selection (age, gender, drug use/abuse habits, HIV status, cancer history)
2. Composition of donor tissue (BMP, other protein content, particle size, and biologics)

**Table 2: Summary of DBM products by carrier**

| Carrier | DBM product |
|---|---|
| Bovine collagen with sodium alginate | Progenix® |
| Bovine collagen (fibrillar) | B-GENIN |
| Bovine collagen (fibrillar) + hydroxyapatite-tricalcium phosphate granules | R-GENIN |
| Calcium Sulfate | AlloMatrix® |
| Calcium-based 45S5 bioactive glass | Origen DBM®/ NanoFuse® |
| Carboxymethylcellulose (CMC) | SureFuse™ II |
| Carboxymethylcellulose (CMC) + cancellous bone | ExFuse™ II |
| Carboxymethylcellulose (CMC) + phosphate buffered saline | OsteoSelect® |
| Collagen (Porcine) | Osteofil® |
| Gelatin (Porcine) | BellaFuse™ Bioset® |
| Gelatin + cortical cancellous bone chips | Opteform® |
| Glycerol | Optium® Vesuvius® |
| Glycerol/Starch | Grafton®/ Grafton Plus® |
| Hydrogel carrier with or without cancellous bone chips | Optecure® |
| Lecithin | InterGro®DBM StaGraft™ |
| Polyglycolic acid resorbable mesh bag | Magnifuse® II |
| Reverse Phase Medium | AlloFuse® DynaGraft™ II |
| Reverse phase medium with Accell bone matrix | Accell Connexus® Accell Evo3™ |
| Reverse phase medium with cancellous bone chips | OrthoBlast™ II |
| Sodium Hylauronate | DBX® |
| DBM with No Carrier | Puros® DBM<br>Accell TBM®<br>DBMPure<br>FUSIONFLEX™<br>H-GENIN™ DBM<br>OsteoSponge®<br>OsteoPro™ DBM100<br>Purebone® |

3. Freeze-dried packaging methods
4. Lot sampling for osteoinductive index
5. Transparency in labeling of such information.

There is significant variability with which present-day DBM products are extracted, processed, and packaged. Demineralized bone matrices are often developed through extraction of cortical allograft bone that subsequently undergoes demineralization via acid extraction, sterilization, and combination with a carrier to prevent migration. However, depending on the preparation methods utilized, each DBM product offers assorted advantages and disadvantages leading to variable fusion rates. These factors not only establish variability between products but may also contribute to intravariability of several characteristics within the same batch of a given DBM product.

Despite the extreme variability in the number and types of DBM products complicating product selection, their efficacy has been proven in treating multilevel cervical disc disease[6] and augmenting spinal fusions in both experimental animals and patients.[8]

One of the objectives of this paper is to elucidate and help unravel the diverse slate of DBM products and the complex process of selecting one for use in patients. Synthesizing the available information and without favoring any one company or distributor, the surgeon-author can make several suggestions, without specific endorsements. These suggestions are based on published information provided, keeping in mind several companies have not fully disclosed the information on exact content and percentage by weight of DBM. Thus, in addition to cost concerns (which vary), and transparency of product content, a hospital and surgeon should be well served with the following abbreviated list of DBM products.

For general routine use of DBM as an adjuvant to autologous bone graft for spinal fusions, the surgeon-author suggests a pure 100% DBM paste without carrier such as H-GENIN™, Accell TBM®, or Puros DBM® [Table 3]. See Table 2 for other options.

In addition, for posterior spinal surgery, the surgeon-author recommends a DBM bone strip, which is soft and porous and offers more immediate support and scaffolding. The strip is especially useful if soaked in an autologous Bone Marrow Aspirate Concentration (BMAC). Among those listed in Table 1, malleable DBM bone strips such as OsteoSponge® or Accell TBM® and H-GENIN™ are recommended [Table 3].

On occasion, there is a need to inject DBM into a bone defect, e.g., when caused by the removal of a Pedicle screw. For this purpose, the surgeon-author proposes using a DBM with a carrier, making it amenable to placement into a syringe and viscous enough to be injected through a syringe and applicator (such as OsteoSponge® syringe, Allomatrix® injectable putty, and OsteoSelect®). See Table 3 for a summary of recommendations and DBM content.

It is difficult to meaningfully select DBM products if the information is not posted on packaging material. Surgeons and hospital systems must "raise the bar" when selecting DBM products. It is the responsibility of companies and the FDA to make available the origin, processing, storage parameters, and the final DBM content of these products. Increased transparency through better labeling will lead to greater knowledge and patient safety. It is also acceptable to have fewer, but better DBM products. Table 4 and

**Table 3: Recommended DBM products based on general use, use for posterior spinal surgery, and use for injectable purposes**

| For general use | For posterior spinal surgery | For injectable purposes | |
|---|---|---|---|
| 100% DBM as an adjuvant to autologous bone graft | Malleable DBM bone strips/bone sponge with 100% DBM | Injectable Putty with High DBM content | |
| **Products** | **Products** | **Products** | **Published %DBM** |
| H-GENIN™ | OsteoSponge® | OsteoSponge® | 100 |
| Accell TBM® | Accell TBM® | Allomatrix® | 86 |
| Puros DBM® | H-GENIN™ | OsteoSelect® | 74 |

**Table 4: Considerations for DBM product selection (surgeons and hospital)**

| Consideration | Particular Issues | |
|---|---|---|
| Safety | • FDA 510(k) approved<br>• Aseptic technique, screened for infection<br>• Legally-obtained bone samples<br>• Non-harmful carrier | |
| Transparency and Accurate Labeling | • Disclose exact source of bone bank (e.g., LifeNet, MTF, etc.)<br>• Disclose processing methods<br>• Proof/verification of FDA compliance<br>• Identify carrier type and percentage of total volume<br>• Osteoinductivity proven for all lots released | |
| **Biological Properties** | **Primary Considerations** | **Secondary Considerations** |
| | • Osteoconductive<br>• Osteoinductive<br>• Osteogenic<br>• Angiogenic | • Contain high % DBM and little to no carrier<br>• Little to no synthetics |
| Physical Properties and Forms | • Graft extender – voluminous, acts as scaffold<br>• Limited migration (adhesive, suturable)<br>• Does not exert harmful force<br>• Conforms to spaces (injectable, moderate viscosity, malleable) | |
| Cost | • Fair market value<br>• Pricing per unit volume as opposed to per case<br>• Price negotiated via ethical business principles<br>• Limit number of vendors but avoid monopoly | |

Figure 1 provide considerations and recommendations for DBM selection, respectively.

## FUTURE DIRECTIONS

In the future, DBM products may be gradually replaced or enhanced by more effective treatment modalities such as autologous stem cells from bone marrow aspirates. The industry has already begun to develop new products promoting greater angiogenesis (adding vascular endothelial growth factor (VEGF) as seen in Bio4®). Other companies propose bone grafts with live stem cells already committed to differentiation into osteocyte lineage (ViviGen® Cellular Bone Matrix). While these newer treatment methods/products are still being developed, there is an immediate need to be equipped to choose the "best" DBM products for our patients.


**Figure 1: Hierarchy of considerations in DBM product selection**

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There are no conflicts of interest.

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