TISSUE PROCESSING MATTERS.

D-MIN™
Aseptic Tissue Demineralization

The Medtronic Eatontown tissue processing facility is a purpose built facility that utilizes state of the art ISO Class 5 Clean Rooms, Onsite Microbiology Labs & Staffed Highly Trained Scientists and Engineers to ensure our tissue grafts have the most inductive and conductive properties on the market today. Our dedication to processing tissue began in 1986. And many of the industry standards that are followed today were established here. Partnering with us for your demineralized bone graft needs will ensure you are giving your patients the best opportunity to heal.
Allograft bone that has undergone demineralization (the process of removing certain minerals and cellular elements) has been shown to be a useful graft material due to its combined osteoconductive and osteoinductive properties.\(^1\,^2\,^3\)

**THE NEXT ADVANCE IN THE EVOLUTION OF ALLOGRAFT TISSUE SCIENCE**

While the effectiveness of demineralized bone matrix in bone defect reconstruction was reported as early as 1889,\(^4\) one of the first documented clinical uses of demineralized bone matrix was reported in 1961 by Sharrard and Collins,\(^5\) who successfully used the material for spinal fusion in children. More recently, Kang et al.\(^6\) proved at a 2-year follow-up subjects who were randomized to Grafton™ Matrix and local bone achieved an 86% overall fusion rate and improvements in clinical outcomes that were comparable with those in the iliac crest bone graft group, which is considered the gold standard for clinicians. All of this information demonstrates how demineralized bone matrix plays an important role in many bone transplant procedures.

**FUSION RATE**

86%

**OVERALL AND IMPROVEMENTS IN CLINICAL OUTCOMES**
In describing the ideal demineralized bone, one should consider the relevant characteristics desired of any allograft material. As such, the ideal demineralized bone matrix would:

- Have ample clinical evidence published in peer-reviewed journals.
- Expose the graft’s inherent biologic potential.
- Minimize the potential immune or inflammatory responses at the graft site.
- Not be a source of infectious disease.
- Be convenient to place and allow for a favorable graft to host interface.
- Be available on a consistent basis in a variety of forms.
All tissues undergoing the D-MIN™ Process are selected from donors following a detailed social and medical history screening, and are recovered using stringent aseptic technique.

Comprehensive serologic testing of donor blood is performed, which includes sensitive testing for HIV, hepatitis, and syphilis, in addition to screening for systemic infections. The tissues are aseptically processed by Medtronic in certified clean rooms where rigorous production standards and quality assurance protocols are applied. D-MIN™ Processing includes many safety-enhancing procedures such as double freeze-thaw cycles, ultrasonic cleaning, antibiotic soaks, the removal of blood and lipids, and complete low moisture levels lyophilization.

For added safety, all tissues are bathed in ethanol, a known virucidal agent. Microbiology tests are performed multiple times prior to and throughout the process.

A published university-based study has found that the D-MIN™ Process inactivates and eliminates HIV in infected human bone.7

It is this combination of stringent donor screening, rigorous testing, and proprietary processing technologies that contributes to safe allograft bone.

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**DONOR SCREENING – TWO STAGES**

**Medical History**
- Interview with Family

**Tissue Bank**
- Medical Director Review

### Decision to Recover
- Yes: Recovery
  - Gather information:
    - Autopsy
    - Physical Examination
    - Swab Culture
    - Serology

### Decision to Process
- Yes: Process tissue
- No: Excluded from processing facility

*eligibility criteria meets or exceeds AATB and FDA requirements*
RELATIVE RISK OF DISEASE TRANSMISSION

The risk of transmitting HIV through an appropriately screened donor population has been reported as less than 1 in 4,669,173,600,000,000.*

< 1 in 4.6 Quadrillion

*More rigorous/selective/sensitive screening methods (questionnaire, testing, etc.) have become available since, further reducing the risk of transmission.


RISK REDUCTION

1. General Population
2. FDA & AATB Guidelines + GTP
3. Donor Acquisition & Selection
4. Plant Controls + Testing
5. Tissue Processing
   5A. Acid Demineralization
   5B. Ethanol Treatment
   5C. Lyophilization

Each step in our aseptic process is designed to reduce the bio burden of the tissue. As tissue-based products move through our processing facility they become cleaner and therefore do not require terminal sterilization.

> 25 YEARS OF CLINICAL HISTORY
STRINGENT DONOR SCREENING AND RIGOROUS TESTING

Microbiology:
- Complete Anaerobe and Aerobe Identification

-70°C (First Freeze Cycle)

Donor Selection

Medical and Social History Screening

Serology:
- HIV-1 Ab, NAT
- HIV-2 Ab
- HBVsAg and NAT
- HBV Ab, NAT
- HCV Ab, NAT
- Syphilis (T. Pallidum)

*Required for international markets only

Medical Director and Quality Assurance (QA) Review

Freezing

Medical Review

Medtronic Process of Pretreatment Irradiation is conducted for selected donors based on bioburden results.

Pretreatment Irradiation

Physical Debridement, Ultrasonic Bath, Ethanol Treatment, Antibiotic Soak, and Blood/Lipid Removal

Physical Processing

Controlled Acid Soak

D-MIN™ Process

Preservation

Lyophilization: Freezing -70°C (Second Freeze Cycle)

Final QA Release


General Population

Medtronic Process of Pretreatment

Medtronic Proprietary Process

Medtronic_process.png
Despite demineralized bone matrix’s long and successful history of clinical performance, Medtronic has identified opportunities to improve the demineralization process. Medtronic has carefully developed the D-MIN™ Process — a controlled demineralization process built upon the foundations laid by Urist, Reddi, Glowacki, and other leading investigators.

Our attention is focused on what matters most to you: bone formation and safety.

10x Magnification of Hematoxylin eosin (H&E) staining of donor matched DBM bone fibers after 28 day implantation in athymic rat muscle pouch model following treatment with either Medtronic’s D-MIN™ process (A) or a common competitive processing solution (B). Residual DBM (red arrows) is easily identified in both groups.

**NOTE**

DBM has been extensively repopulated with new cells and is associated with new bone deposition (green arrows), as well as mature bone marrow development (yellow arrows) following Medtronic’s D-MIN™ process (A) compared to a common competitive processing solution (B) where the cellular response is predominately encapsulation and/or infiltration of the DBM by fibrous connective tissue (black arrows).

Medtronic’s D-MIN™ treatment effectively maintains the activity of DBM enabling improved in vivo bone formation as compared to other common competitive processing solutions.

- Red arrows indicate residual DBM. 10x Magnification
- Green arrows indicate new bone deposits. 10x Magnification
- Yellow arrows indicate bone marrow development. 10x Magnification
- Black arrows indicate fibrous connective tissue. 10x Magnification
Because allograft tissue processing, including demineralization, has evolved over time and is performed by numerous processors, it is important to recognize that not all demineralization processes are alike. Process variables include:

- Acid application
- Temperature
- Demineralization time
- Application of defatting agents such as ethanol
- Aseptic processing methods versus those employing ethylene oxide or terminal sterilization

These variables may affect the processed tissue in multiple ways, including the levels of residual calcium, hydrochloric acid (HCl), and moisture, and thus may impact the performance and safety of the graft. Hence, it is imperative to control each aspect of the demineralization treatment through a validated process.
Animal testing is not necessarily indicative of human clinical outcome.


Data on File from Medtronic internal testing (11/2016):

Grafton™ DBM products, Magnifuse™ Bone Graft, Xpanse™ Bone Insert, Mastergraft™ Matrix ongoing final product testing (2006-2014); Accell Connexus®, three manufacturing lots tested on 2005; Accell Evo3®c, three manufacturing lots tested on 2010/2014; Intergro® Putty, one manufacturing lot tested on 2004; Accell TBM®, two manufacturing lots tested on 2010; DBX® Strip, three manufacturing lots tested on 2010; DBX® Mix, two manufacturing lots tested on 2010; DynaGraft® II, one manufacturing lot tested on 2003; Allomatrix® DBM, five manufacturing lots tested on 1999/2005; OrthoBlast® II DBM Putty, two manufacturing lots tested on 2003/2005; Accell DBM 100, two manufacturing lots tested on 2003/2005; OsteoSet® 2 DBM, two manufacturing lots tested on 2008; Osteocel® Plus, four manufacturing lots tested on 2011-16; Osteocel® Pro, three manufacturing lots tested on 2016; Puros® one manufacturing lot tested on 2010.

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**Grafton™ and Grafton Plus™ Demineralized Bone Matrix (DBM)**

**Indications**

Grafton™ DBM and Grafton Plus™ DBM are intended for use as a bone graft extender, bone graft substitute, and bone void filler in bony voids or gaps of the skeletal system (i.e., spine, pelvis, and extremities) not intrinsic to the stability of the bony structure. The voids or gaps may be surgically created defects or defects created by traumatic injury to the bone. Grafton™ DBM (excluding the Orthoblend form) and Grafton Plus™ DBM are also intended to be packed into bony voids or gaps to fill and/or augment dental intraosseous, oral, and cranio-/maxillofacial defects. These defects may be surgically created osseous defects or osseous defects created from traumatic injury to the bone, including periodontal/infrabony defects; alveolar ridge augmentation (sinusotmy, osteotomy, cystectomy); dental extraction sites (ridge maintenance, implant preparation/placement); sinus lifts; cystic defects; craniofacial augmentation. Grafton™ DBM and Grafton Plus™ DBM may be used alone in a manner comparable to autogenous bone chips or allograft bone particulate (demineralized freeze dried bone), or they may be mixed with either allograft or autograft bone or bone marrow as a bone graft extender. Grafton™ DBM and Grafton Plus™ DBM are indicated only for bony voids or gaps not intrinsic to the stability of the bony structure. Grafton™ DBM and Grafton Plus™ DBM are absorbed/remodeled and replaced by host bone during the healing process. Note: The user should consider the fact that Grafton™ DBM CRUNCH™ contains demineralized bone chips approximately 3 mm (±1 mm) in determining the appropriateness of this allograft for use in small defects.

**Contraindications**

The following are contraindications for the use of Grafton™ DBM and Grafton Plus™ DBM:

- The presence of infection at the transplantation site.
- Treatment of spinal insufficiency fractures.

**Caution**

This allograft may contain trace amounts of antibiotics (gentamicin), surfactant, and other processing solutions. Caution should be exercised if the patient is allergic to these antibiotics or chemicals. Grafton Plus™ DBM Paste contains starch. Therefore, caution should be exercised in using Grafton Plus™ DBM Paste in a patient with a starch allergy and/or amylase deficiency.

**Magnifuse™ II DBM Products**

**Indications**

Intended for use as a bone graft substitute in bony voids or gaps of the skeletal system (i.e., spine, pelvis and extremities) not intrinsic to the stability of the bony structure. The voids or gaps may be surgically created defects or defects created by traumatic injury to the bone. Magnifuse™ II DBM may be used in a manner comparable to autogenous bone or allograft bone. Magnifuse™ II DBM may be mixed with fluid such as bone marrow aspirate, blood, sterile water, or sterile saline in order to adjust the consistency and handling characteristics of the bone graft material.

**Contraindications**

The following are contraindications for the use of Magnifuse™ II DBM:

- The presence of infection at the transplantation site.
- Treatment of spinal insufficiency fractures.

**Caution**

This product may contain trace amounts of antibiotics (gentamicin), surfactant, and other solutions used in processing the bone tissue as well as the PGA mesh. Caution should be exercised if the patient is allergic to these antibiotics or chemicals.

**Magnifuse™ Bone Graft Products**

**Indications**

Intended for use as a bone graft substitute in bony voids or gaps of the skeletal system (i.e., spine, pelvis and extremities) not intrinsic to the stability of the bony structure. The voids or gaps may be surgically created defects or defects created by traumatic injury to the bone. Magnifuse™ Bone Graft may be mixed with fluid such as bone marrow aspirate, blood, sterile water, or sterile saline in order to adjust the consistency and handling characteristics of the bone graft material.

**Contraindications**

The following are contraindications for the use of Magnifuse™ Bone Graft:

- The presence of infection at the transplantation site.
- Treatment of spinal insufficiency fractures.

**Caution**

This product may contain trace amounts of antibiotics (gentamicin), surfactant, and other solutions used in processing the bone tissue as well as the PGA mesh. Caution should be exercised if the patient is allergic to these antibiotics or chemicals.

**Grafton™ DBM DBF Products**

Grafton™ DBM DBF can be used in orthopedic or reconstructive bone grafting procedures. The product can also be used in bone grafting procedures in combination with autologous bone or other forms of allograft bone, or alone as a bone graft.

**Contraindications**

The presence of infection at the transplantation site is a contraindication for the use of this allograft.

**Caution**

This allograft may contain trace amounts of antibiotics (gentamicin), surfactant, and other processing solutions. Caution should be exercised if the patient is allergic to these antibiotics or chemicals.

**Precautions**

Despite the viral inactivation and extensive tissue donor selection and qualification processes used in providing this tissue graft (see DONOR SCREENING AND TESTING), transmission of a communicable disease through the use of this tissue graft is still possible. Bacterial infection at the graft site may also occur. Any adverse outcomes potentially attributable to Grafton™ DBM DBF must be reported promptly to Medtronic.
**Progenix™ Putty and Progenix™ Plus**

**Indications**

Progenix™ Putty is intended for use as a bone graft substitute in bony voids or gaps of the skeletal system not intrinsic to the stability of the bony structure (i.e. spine, pelvis and extremities). The voids or gaps may be surgically created osseous defects or osseous defects created from traumatic injury to the bone. Progenix™ Putty provides a bone void filler that is resorbed/remodeled and is replaced by host bone during the healing process. When used in the extremities or pelvis, the device is used by itself. When used in the spine, the device must be mixed with autograft bone and used as a bone graft extender. Progenix™ Plus is intended for use as a bone graft substitute in bony voids or gaps of the skeletal system not intrinsic to the stability of the bony structure (i.e. spine, pelvis and extremities). The voids or gaps may be surgically created osseous defects or osseous defects created from traumatic injury to the bone. Progenix™ Plus provides a bone void filler that is resorbed/remodeled and is replaced by host bone during the healing process. The device may either be used alone or mixed with autograft bone and used as a bone graft extender.

**Contraindications**

These products are contraindicated, and should not be used, in patients who have known allergies to bovine collagen, sodium alginate or polymyxin and/or bacitracin antibiotics. These products do not possess sufficient mechanical strength to support the reduction of a defect site prior to soft and hard tissue ingrowth. These products are contraindicated where stabilization of the defect is not possible.

**Warnings and Precautions**

A small number of patients may experience localized immunological reactions resulting from the use of this device (e.g. transient localized edema and swelling, and rash.) The safety and effectiveness of the device in these patients has not been established.

Over-pressurizing the device may result in extrusion beyond the site of its intended application and may damage the surrounding tissues.

Over-pressurizing the defect site may lead to fat embolization or embolization of the device’s material into the bloodstream.

**Xpanse™ Bone Insert**

Xpanse™ Bone Insert is comprised of demineralized allograft and can be used in orthopedic or reconstructive bone grafting procedures. The product can also be used in bone grafting procedures in combination with autologous bone or other forms of allograft bone, or alone as a bone graft. The presence of infection at the transplantation site is a contraindication for the use of this allograft.
REFERENCES


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