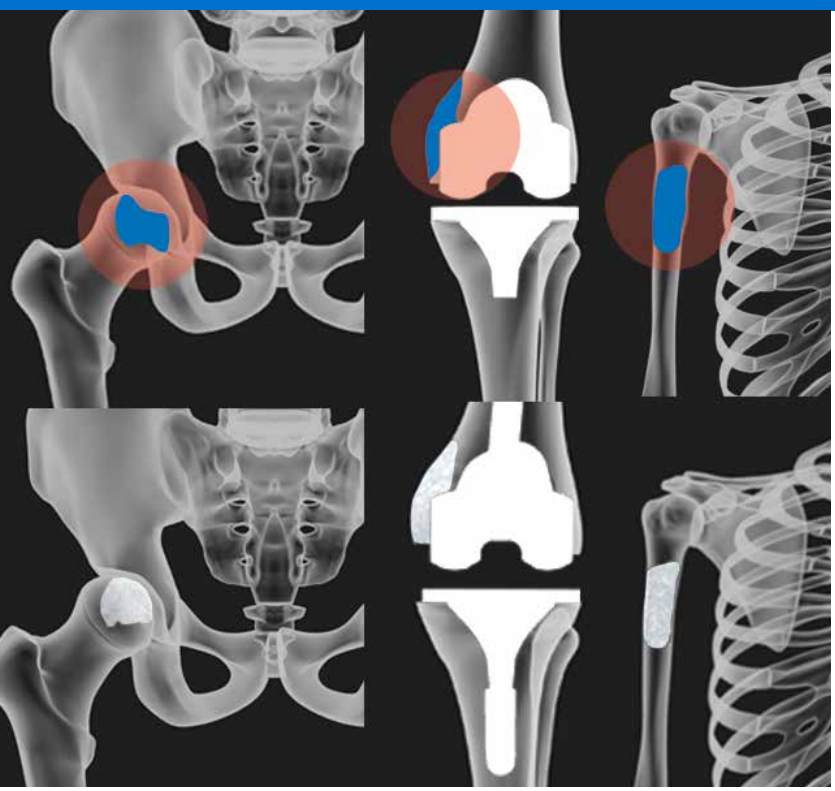
EXACTECH | **BIOLOGICS**



# Exactech Tissue Standards

Hospital Information Guide

Exactech®

# Exactech Biologics

Exactech recognizes the growing importance of biologics in bone repair and regeneration. We are developing a position of leadership by designing and acquiring the broadest range of biomaterials, delivery systems and surgical techniques while providing innovative, surgeon-driven solutions that are intended to mimic the body's tissue environment.

**Allograft DBM**

Optecure®

**Allograft DBM +CCC**

Opteform

Optecure®+CCC

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# The Tissue Bank Defined

## The Tissue Bank

To promote successful surgical outcomes, surgeons may rely on biomedical tissues or human tissues and organs for transplantation. These donated tissues are readied for implantation at tissue banks. Since 1993, any human tissue intended for transplantation has been regulated by the Food and Drug Administration (FDA).[1-3]

# Food and Drug Administration

The FDA maintains the final rule for transplantable tissue, the Current Good Tissue Practice for Human Cell, Tissue and Cellular and Tissue-Based Product Establishments (HCT/P), Inspection and Enforcement. These mandatory practices either directly prevent the introduction, transmission or spread of communicable diseases, or support such a requirement. All establishments that manufacture HCT/P must comply with the Current Good Tissue Practice (CGTP) Guidelines.

The Federal recommendations for Tissue Processing Standards are detailed and extensive. These standards require that tissue banks design a quality program to maintain procedures for the following functions: [4,5]

- Recovery
- Donor screening
- Donor testing
- Exclusion criteria
- Material processing
- Storage
- Labeling
- Packaging
- Distribution
- Quality program

These actions are intended to improve protection of the public health while keeping regulatory burden to a minimum, which in turn would encourage significant innovation.

All tissue banks must comply with these standards and are subject to:

- Audits
- Inspections
- Enforcements

# American Association of Tissue Banks

- Non-Profit Professional Organization
- Tax-exempt status as a Scientific and Educational Organization
- Founded in 1976 by the same medical and research professionals who started the nation's first tissue bank in 1949, the US Navy Tissue Bank.

### Purpose and Mission[1,2]

The AATB is dedicated to ensuring human tissues intended for transplantation are:

- Safe
- Free of infectious disease
- Available in quantities sufficient to meet national needs

The AATB has published the only authoritative industry standard for tissue banks since 1984.

### AATB Programs

Voluntary Accreditation Program

- Offered since 1986
- Ensures that tissue banking activities are performed in a professional manner
- Maintains compliance with Tissue Processing standards

# The AATB

**Certification Program**[1,2]

- Initiated in 1987
- Membership includes:
  - More than 1,100 individuals
  - 3,000 Certified Tissue Bank Specialists (CTBS) worldwide
  - 1,800 active and certified members
- More than 100 accredited tissue banks in US and Canada
  - Banks recover tissue from more than 25,000 donors and distribute in excess of 2 million allografts for transplant annually (2007).

# Exactech Tissue Standards

Exactech donor tissue is obtained from AATB accredited tissue banks. Donor suitability is determined in accordance with AATB standards and FDA regulations.

Exactech's primary goal is to ensure patient safety. To fulfill this goal, Exactech employs stringent tissue testing to significantly diminish the potential for disease transmission. These redundant safeguards provide the highest level of confidence that patients will receive safe, high-quality tissue. The safety of tissue is contingent on donor screening, testing and tissue preparation.

**Donor Screening and Testing**

After consent for donation is obtained, potential donors are screened for risk factors associated with infectious diseases and medical conditions. This screening includes physical evaluation of the donor, an interview with a person who knew the donor, review of available medical records and review of autopsy findings (when applicable).

In accordance with FDA regulations and AATB guidelines, potential donors are tested for the following:

- Hepatitis B Surface Antigen (HBsAg)
- Total antibody to Hepatitis B core antigen (anti-HBc-total meaning IgG and IgM)
- Human Immunodeficiency Virus antibody (anti-HIV-1 and anti-HIV-2)
- Nucleic acid test (NAT) for HIV-1
- Human T-lymphotrophic virus type I and II antibody (anti-HTLV-I and anti-HTLV-II)
- Antibody to Hepatitis C Virus (HCV)
- Nucleic acid test (NAT) for HCV
- Rapid Plasma Reagin or Serological Tests for Syphilis

If the potential donor tests positive for any of the above conditions, then he or she is excluded from donation.

# Exactech Tissue Standards

In addition to the general exclusion criteria, the following medical conditions shall also preclude musculoskeletal tissue donation:

- Rheumatoid arthritis
- Systemic lupus erythematosus
- Polyarteritis nodosa
- Sarcoidosis
- Clinically significant metabolic bone disease

**Processing**

Exactech's allograft is processed using aseptic techniques that guard against contamination. Additionally, Exactech's allograft is produced using processes demonstrated to reduce viral contamination.

## Exactech Registration

- Tissue Bank License in all required states including:
  - California
  - Florida
  - Maryland
  - New York

# Material Design Criteria

Biologic materials should provide for the greatest potential of new bone formation with unyielding safety assurances. Exactech materials are engineered with:

- Scientific design rationales
- DBM concentration studies[6]
- Clinically utilized constituents
- Unique flexibility
- Superb handling characteristics
- Carrier technologies that resist migration[6]

# Osteoinductive Testing

Osteoinduction is typically associated with the presence of growth factors within the graft material. Since demineralized bone matrix contains the cocktail of naturally occurring Bone Morphogenetic Proteins, it is the principal component to provide for the osteoinductive element in natural human bone allografts.

## Preserving the Proteins in DBM

Preserving the biologics function of bone proteins while reducing the potential for disease transmission is a delicate balance. To ensure that Exactech provides only viable materials, every lot of DBM is screened for osteoinductive potential through in-vivo testing of the formulated product. Exactech allografts are delivered lyophilized to ensure the bone-forming proteins do not denature during storage.

## Testing for Osteoinductive Potential

Using the modified Urist model to verify osteoinductive potential, the bone graft material is prepared and implanted in an athymic nude mouse. Later, the bony ossicle is explanted and observed through histology and scored for endochondral bone formation. Findings from the animal model are not necessarily predictive of human clinical results.

# Osteoinductive Testing

## The In-Vivo Process

### STEP 1

- Samples from every donor lot are formulated with the carrier and tested for osteoinductive potential post processing.

### STEP 2

- In-vivo implantation in a heterotopic site in athymic nude mouse.

### STEP 3

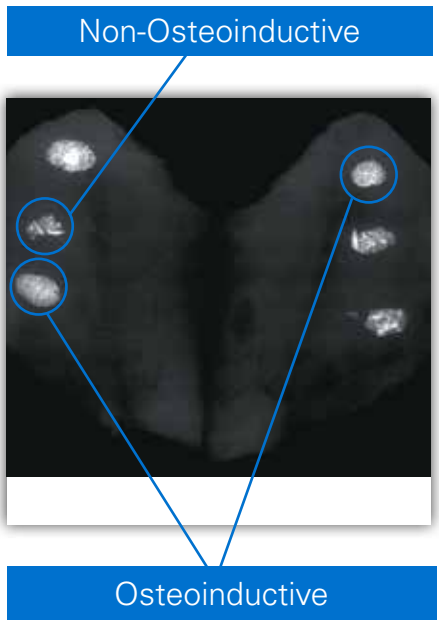
- Explants are evaluated histologically for new bone formation.

### STEP 4

- Stringent bone growth requirements must be met.

# 100 Percent Inductivity Quality Control

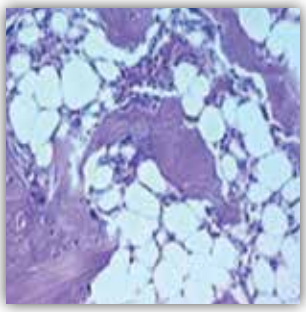
Some DBM does not induce new bone formation and will be excluded from Exactech bone graft materials.




The ossicle is explanted and evaluated according to established criteria for new bone formation.

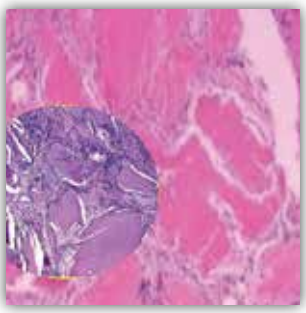
# 100 Percent Inductivity Quality Control

**Inductive DBM**



- New bone deposition
- Active osteocytes (mature osteoblasts)
- Organized bone marrow
- Minimal cellular infiltrate

**Non-Inductive DBM**
(Inflammatory Response)

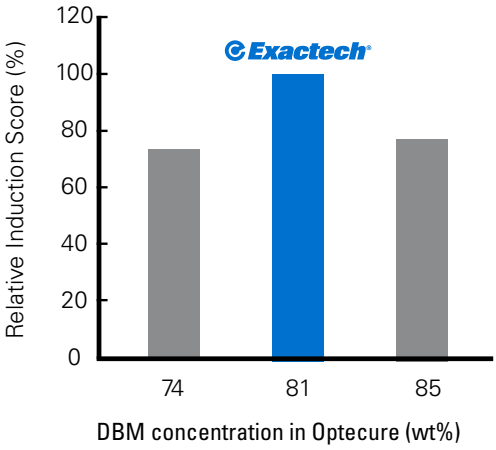


- Giant cells/ osteoclasts (bone resorbing cells)
- Varying levels of fibrosis
- Dense cellular infiltrate

# DBM Concentration

DBM concentration (dose) may be the single, most critical engineering variable in bone graft material design. The study, using DBM formulated with a hydrogel carrier, demonstrated optimum new bone formation dependency at specific DBM concentration.[6]

**Osteoinduction Potential as Compared to the Positive DBM Control Alone -Resorbable Hydrogel Carrier**



# Providing an Effective Conductive Lattice

Osteoconductive properties are determined by the presence of a scaffold that is an effective three-dimensional lattice intended for mechanical load sharing and a structure for new bone cells to migrate on and through.

- Cancellous bone provides a favorable porous environment for bone cell migration and attachment.
- Cortical bone provides integrity and load-sharing properties.[7]

**Exactech designed inductive DBM materials that offer an optimized conductive lattice, which includes:**

- A high content of cortical and cancellous bone chips that promotes remodeling of the allograft
- A porous cancellous bone for vascularization
- Specifically sized bone chips that are intended to facilitate conversion to host bone as the bone remodels.[6]

# 510(k) Clearance Information

These bone grafting products are classified by the FDA as medical devices and must achieve 510(k) clearance status prior to marketing in the US.

These medical devices may be cleared as bone void fillers, bone graft extenders or bone graft substitutes for use in the extremities, pelvis, spine or any combination.

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