iFACTOR®

THE **ONLY** BONE GRAFT POWERED BY

P15™ osteogenic cell binding peptide

# VAC Pack Appendix

## *Class III Drug-Device Combination Product Approved for Use in the Cervical Spine with Published Level 1 Human IDE Study Data*

*Created for Value Analysis Committee*

CERAPEDICS

*Enhancing the Science of Bone Repair*

# TABLE OF CONTENTS



1 Pivotal IDE study that led to PMA approval for use in spine.

2 i-FACTOR Bone Graft was evaluated in a 319-patient, prospective, randomized, controlled, multi-center clinical trial assessing its safety and efficacy compared to standard-of-care (autograft).

# FDA LETTER FOR PMA P140019

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

Cerapedics, Incorporated
Mr. Roger N. White
Clinical and Regulatory Affairs
11025 Dover Street Suite 1600
Westminster, Colorado 80021

Re: P140019
i-FACTOR Peptide Enhanced Bone Graft
Filed: August 27, 2014
Amended: February 13, May 20, and June 9, 2015
Procode: NOX

Dear Mr. White:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the i-FACTOR Peptide Enhanced Bone Graft. This combination product is indicated for use in skeletally mature patients for reconstruction of a degenerated cervical disc at one level from C3-C4 to C6-C7 following single-level discectomy for intractable radiculopathy (arm pain and/or a neurological deficit), with or without neck pain, or myelopathy due to a single-level abnormality localized to the disc space, and corresponding to at least one of the following conditions confirmed by radiographic imaging (CT, MRI, X-rays): herniated nucleus pulposus, spondylosis (defined by the presence of osteophytes), and/or visible loss of disc height as compared to adjacent levels, after failure of at least 6 weeks of conservative treatment. i-FACTOR Peptide Enhanced Bone Graft P-15 Putty must be used inside an allograft bone ring and with supplemental anterior plate fixation. We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). The device is further restricted under section 515(d)(1)(B)(ii) of the act insofar as the labeling must specify the specific training or experience practitioners need in order to use the device. FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Expiration dating for this device has been established and approved at 3 years. This is to advise you that the protocol you used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(7).

Click here to view and/or download the complete FDA Letter for PMA P140019

or type cerapedics.com/IF_FDAapproval into your browser.

i-FACTOR® Peptide Enhanced Bone Graft

CERAPEDICS
*Enhancing the Science of Bone Repair*

**INSTRUCTIONS FOR USE**

CAUTION: Federal (United States) law restricts this device to sale by or on the order of a physician.

**DEVICE DESCRIPTION:**

i-FACTOR® Peptide Enhanced Bone Graft (also referred to as i-FACTOR® Bone Graft or i-FACTOR® Putty) is a composite bone graft material consisting of multiple components - a synthetic peptide (P-15) adsorbed onto calcium phosphate particles, which are suspended in a hydrogel carrier. The i-FACTOR Peptide Enhanced Bone Graft must be used in combination with an allograft ring and a metallic anterior cervical plate.

**i-FACTOR Peptide Enhanced Bone Graft peptide component**

The synthetic peptide is a short chain peptide consisting of 15 amino acids that mimics the sequence of amino acids found in residues 766-780 of the α1 chain of Type I collagen according to the following sequence:

Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val

It is intended to facilitate attachment of osteogenic cells to the granule component. None of the amino acids used in synthesizing the peptide are animal-derived.

**Calcium phosphate granule component**

The calcium phosphate granules, also known as anorganic bone mineral (ABM), provide a scaffolding and source of calcium for new bone growth. These granules consist of hydroxyapatite that is derived from thermally treated (> 1000° C) bovine bone. The thermal processing removes all of the organic material from the source bone. The potential for disease transmission from this component is mitigated by the thermal processing, as well as use of a closed, documented US herd. The granules are irregularly-shaped with a particle diameter range of 250-425µm and are naturally porous.

**Hydrogel component**

The hydrogel component consists of plant-derived sodium carboxymethycellulose (NaCMC) in combination with glycerin and water.

The various components are combined in a proportion that delivers the desired handling characteristics and allows the material to be maintained at the surgical site. Prior to being combined with the hydrogel component, the peptide component is adsorbed onto the calcium phosphate granules component. The final composition of i-FACTOR Peptide Enhanced Bone Graft is shown in the following table:

*(continued in link below)*

Click here to view and/or download the complete Current IFU

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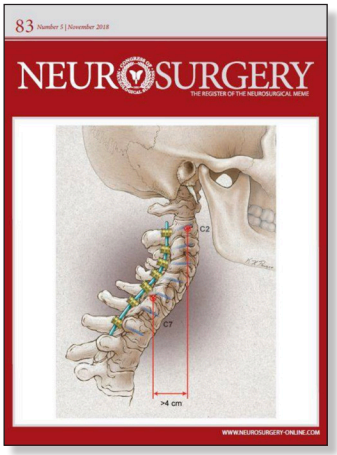
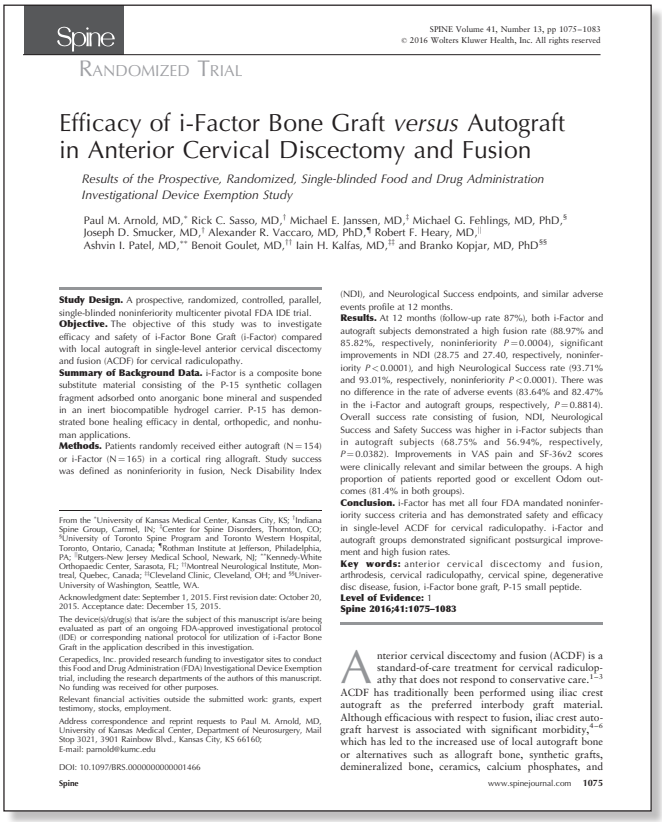
# PUBLISHED CLINICAL STUDIES (1 & 2 YEARS)

Spine

SPINE Volume 41, Number 13, pp 1075–1083


RANDOMIZED TRIAL

## Efficacy of i-Factor Bone Graft *versus* Autograft in Anterior Cervical Discectomy and Fusion

*Results of the Prospective, Randomized, Single-blinded Food and Drug Administration Investigational Device Exemption Study*

Paul M. Arnold, MD,* Rick C. Sasso, MD,† Michael E. Janssen, MD,‡ Michael G. Fehlings, MD, PhD,§ Joseph D. Smucker, MD,‖ Alexander R. Vaccaro, MD, PhD,¶ Robert F. Heary, MD,‖ Ashvin I. Patel, MD,** Benoit Goulet, MD,†† Iain H. Kalfas, MD,‡‡ and Branko Kopjar, MD, PhD§§

**Study Design.** A prospective, randomized, controlled, parallel, single-blinded noninferiority multicenter pivotal FDA IDE trial.
**Objective.** The objective of this study was to investigate efficacy and safety of i-Factor Bone Graft (i-Factor) compared with local autograft in single-level anterior cervical discectomy and fusion (ACDF) for cervical radiculopathy.
**Summary of Background Data.** i-Factor is a composite bone substitute material consisting of the P-15 synthetic collagen fragment adsorbed onto anorganic bone mineral and suspended in an inert biocompatible hydrogel carrier. P-15 has demonstrated bone healing efficacy in dental, orthopedic, and nonhuman applications.
**Methods.** Patients randomly received either autograft (N = 154) or i-Factor (N = 165) in a cortical ring allograft. Study success was defined as noninferiority in fusion, Neck Disability Index (NDI), and Neurological Success endpoints, and similar adverse events profile at 12 months.
**Results.** At 12 months (follow-up rate 87%), both i-Factor and autograft subjects demonstrated a high fusion rate (88.97% and 85.82%, respectively, noninferiority $P = 0.0004$), significant improvements in NDI (28.75 and 27.40, respectively, noninferiority $P < 0.0001$), and high Neurological Success rate (93.71% and 93.01%, respectively, noninferiority $P < 0.0001$). There was no difference in the rate of adverse events (83.64% and 82.47% in the i-Factor and autograft groups, respectively, $P = 0.8814$). Overall success rate consisting of fusion, NDI, Neurological Success and Safety Success was higher in i-Factor subjects than in autograft subjects (68.75% and 56.94%, respectively, $P = 0.0382$). Improvements in VAS pain and SF-36v2 scores were clinically relevant and similar between the groups. A high proportion of patients reported good or excellent Odom outcomes (81.4% in both groups).
**Conclusion.** i-Factor has met all four FDA mandated noninferiority success criteria and has demonstrated safety and efficacy in single-level ACDF for cervical radiculopathy. i-Factor and autograft groups demonstrated significant postsurgical improvement and high fusion rates.
**Key words:** anterior cervical discectomy and fusion, arthrodesis, cervical radiculopathy, cervical spine, degenerative disc disease, fusion, i-Factor bone graft, P-15 small peptide.
**Level of Evidence:** 1
**Spine 2016;41:1075–1083**

From the *University of Kansas Medical Center, Kansas City, KS; †Indiana Spine Group, Carmel, IN; ‡Center for Spine Disorders, Thornton, CO; §University of Toronto Spine Program and Toronto Western Hospital, Toronto, Ontario, Canada; ¶Rothman Institute at Jefferson, Philadelphia, PA; ‖Rutgers-New Jersey Medical School, Newark, NJ; **Kennedy-White Orthopaedic Center, Sarasota, FL; ††Montreal Neurological Institute, Montreal, Quebec, Canada; ‡‡Cleveland Clinic, Cleveland, OH; and §§University of Washington, Seattle, WA.

Acknowledgment date: September 1, 2015. First revision date: October 20, 2015. Acceptance date: December 15, 2015.
The device(s)/drug(s) that is/are the subject of this manuscript is/are being evaluated as part of an ongoing FDA-approved investigational protocol (IDE) or corresponding national protocol for utilization of i-Factor Bone Graft in the application described in this investigation.
Cerapedics, Inc. provided research funding to investigator sites to conduct this Food and Drug Administration (FDA) Investigational Device Exemption trial, including the research departments of the authors of this manuscript. No funding was received for other purposes.
Relevant financial activities outside the submitted work: grants, expert testimony, stocks, employment.
Address correspondence and reprint requests to Paul M. Arnold, MD, University of Kansas Medical Center, Department of Neurosurgery, Mail Stop 3021, 3901 Rainbow Blvd., Kansas City, KS 66160;
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DOI: 10.1097/BRS.0000000000001466

Anterior cervical discectomy and fusion (ACDF) is a standard-of-care treatment for cervical radiculopathy that does not respond to conservative care.[1–3] ACDF has traditionally been performed using iliac crest autograft as the preferred interbody graft material. Although efficacious with respect to fusion, iliac crest autograft harvest is associated with significant morbidity,[4–6] which has led to the increased use of local autograft bone or alternatives such as allograft bone, synthetic grafts, demineralized bone, ceramics, calcium phosphates, and





## i-Factor™ Bone Graft vs Autograft in Anterior Cervical Discectomy and Fusion: 2-Year Follow-up of the Randomized Single-Blinded Food and Drug Administration Investigational Device Exemption Study

**Paul M. Arnold, MD***
**Rick C. Sasso, MD#**
**Michael E. Janssen, DO§**
**Michael G. Fehlings, MD, PhD¶**
**Robert F. Heary, MD‖**
**Alexander R. Vaccaro, MD, PhD#**
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**Received,** August 10, 2016.
**Accepted,** August 9, 2017.
**Published Online,** September 8, 2017.



**BACKGROUND:** i-Factor™ Bone Graft (Cerapedics Inc, Westminster, Colorado) is a composite bone substitute material consisting of P-15 synthetic collagen fragment adsorbed onto anorganic bone mineral suspended in an inert biocompatible hydrogel carrier. A pivotal, noninferiority, US FDA Investigational Device Exemption study demonstrated the benefits of i-Factor™ compared to local autograft bone in single-level anterior cervical discectomy and fusion at 1-yr postoperative.
**OBJECTIVE:** To report 2-yr follow-up.
**METHODS:** Subjects randomly received either autograft (n = 154) or i-Factor™ (n = 165) in a cortical ring allograft and followed using radiological, clinical, and patient-reported outcomes.
**RESULTS:** At 2 yr, the fusion rate was 97.30% and 94.44% in i-Factor™ and autograft subjects, respectively ($P = .2513$), and neurological success rate was 94.87% (i-Factor™) and 93.79% (autograft; $P = .7869$). Neck Disability Index improved 28.30 (i-Factor™) and 26.95 (autograft; $P = .1448$); Visual Analog Scale arm pain improved 5.43 (i-Factor™) and 4.97 (autograft) (p = .2763); Visual Analog Scale neck pain improved 4.78 (i-Factor™) and 4.41 (autograft; $P = .1652$), Short Form-36 (SF-36v2) Physical Component Score improved 10.23 (i-Factor™) and 10.18 (autograft; $P = .4507$), and SF36v2 Mental Component Score improved 7.88 (i-Factor™) and 7.53 (autograft; $P = .9872$). The composite endpoint of overall success (fusion, Neck Disability Index improvement >-15, neurological success, and absence of re-operations) was greater in i-Factor™ subjects compared to autograft subjects (69.83% and 56.35%, respectively, $P = .0302$). Twelve (7.45%) i-Factor™ subjects and 16 (10.53%) autograft subjects underwent re-operation ($P = .3411$). There were no allergic reactions associated with i-Factor™.
**CONCLUSION:** Use of i-Factor™ in anterior cervical discectomy and fusion is effective and safe, and results in similar outcomes compared to local autograft bone at 2 yr following surgery.
**KEY WORDS:** i-Factor™ bone graft, P-15 synthetic collagen fragment, Autograft, ACDF

*Neurosurgery 83:377–384, 2018* DOI:10.1093/neuros/nyx432 www.neurosurgery-online.com

Anterior cervical discectomy and fusion (ACDF) is a standard-of-care treatment for cervical radiculopathy that does not respond to nonoperative care.[1–3] ACDF has traditionally been performed using iliac crest autograft, local

**ABBREVIATIONS: ACDF,** anterior cervical discectomy and fusion; **AE,** adverse event; **ANCOVA,** analysis of covariance; **CT,** computed tomography; **DDD,** degenerative disc disease; **FDA,** Food and Drug Administration; **IDE,** Investigational Device Exemption; **MCS,** mental component summary; **NDI,** Neck Disability Index; **PCS,** physical component summary; **SCB,** substantial clinical benefit; **SF-36,** Short Form 36; **VAS,** Visual Analog Scale



### *Randomized Single-Blinded FDA Study*

*Efficacy of i-Factor Bone Graft versus Autograft in Anterior Cervical Discectomy and Fusion*

Published in **Spine**

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### *2-Year Follow-up*

*i-Factor™ Bone Graft vs Autograft in Anterior Cervical Discectomy and Fusion*

Published in **Neurosurgery Journal**

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# THE BURDEN OF PROOF


## MECHANISM OF ACTION

**THE SYNTHETIC P-15 PEPTIDE IN i-FACTOR PEPTIDE-ENHANCED BONE GRAFT RESULTS IN HIGHER EXPRESSION OF ALKALINE PHOSPHATASE (AN EARLY MARKER OF CELL PROLIFERATION) COMPARED TO OTHER BONE GRAFT SUBSTITUTES.**


- Kübler A, Neugebauer J, Oh JH, Scheer M, Zöller JE. Growth and proliferation of human osteoblasts on different bone graft substitutes: an in vitro study. Implant Dentistry. 2004 June : 13(2) :171-9.


**THE SYNTHETIC P-15 PEPTIDE IN i-FACTOR PEPTIDE-ENHANCED BONE GRAFT ENHANCES BONE MARROW STROMAL CELL ATTACHMENT, SPREADING AND ALIGNMENT, AND THE PROVISION OF BIOMIMETIC MICROENVIRONMENTS FOR OSTEOBLASTS LEADING TO BONE FORMATION.**


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J Biomed Mater Res. 1996 Aug;31(4):545-54.

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**THE SYNTHETIC P-15 PEPTIDE IN I-FACTOR PEPTIDE-ENHANCED BONE GRAFT CAUSES STEM CELL DIFFERENTIATION TO VIABLE OSTEOGENIC CELLS.**

*(continued in link below)*

Click here to view and/or download the complete **Burden of Proof** document
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**Cerapedics, Inc.**
**11025 Dover St., Suite 1600, Westminster, Colorado 80021**

## MATERIAL SAFETY DATA SHEET

Complies with OSHA's Hazard Communication Standard
29 CFR 1910.1200

| **Material Identity:** | **i≡FACTOR™ Putty** |
|---|---|

| **SECTION I – Manufacturer Information** | |
|---|---|
| **Manufacturers Name**: *Cerapedics, Inc.* | **Emergency/Information Telephone Number**: *(303) 974-6275* |
| **Address:** *11025 Dover St., Suite 1600, Westminster, CO 80021* | **Date MSDS was Prepared**: October 20, 2009 |

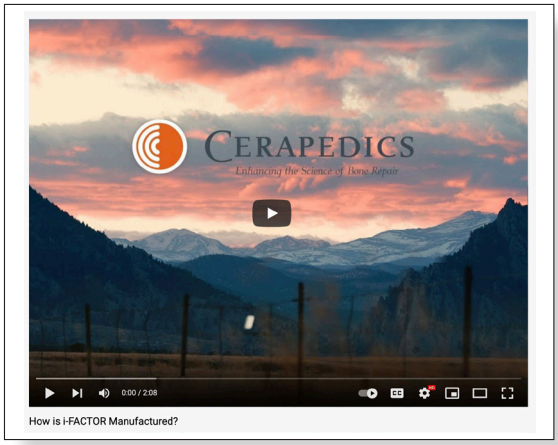
| **SECTION II – Ingredients and Hazards** | **%** | **Hazard Data** |
|---|---|---|
| Hydroxylapatite $Ca_{10}(OH)_2(PO_4)_6$ | 51.94 | No TLV Est. |
| P-15 Peptide $(C_{59}H_{100}N_{20}O_{19}ACOH)$ | $0.3 \times 10^{-6}$ | No TLV Est. |
| Sodium Carboxymethylcellulose $R\ OCH_2\ COONa$ | 1.51 | No TLV Est. |
| Glycerol $C_3H_5(OH)_3$ | 6.98 | No TLV Est. |
| Water for Injection $H_2O$ | 39.57 | No TLV Est. |

| **SECTION III - Physical/Chemical Characteristics** | |
|---|---|
| **Chemical Formula**: See Section II | **Specific Gravity (H20 = 1)**: Particles: *3.14 g/cc Gel Carrier: 1.0 g/cc, Overall: 1.55 g/cc* |
| **Vapor Pressure (mm Mg.)**: *No data* | **Melting Point**: *Particles:1670℃* |
| **Vapor Density (AIR = 1)**: *No data* | **Evaporation Rate**: *No data* |
| **Solubility in Water**: *Particles Practically insoluble. Gel Carrier is water-soluble.* | **Boiling Point**: *No data* |
| **Appearance and Odor**: *White solid granules suspended in a water based gel carrier / no odor.* | |

| **SECTION IV - Fire and Explosion Hazard Data** | |
|---|---|
| **Flash Point (method used)**: *No data* | **Flammable Limits**: *No data* |
| **Extinguishing Methods**: *No data* | |
| **Special Fire Fighting Procedures:** *No special fire fighting procedures needed.* | |
| **Unusual Fire and Explosion Hazards:** *No data* | |

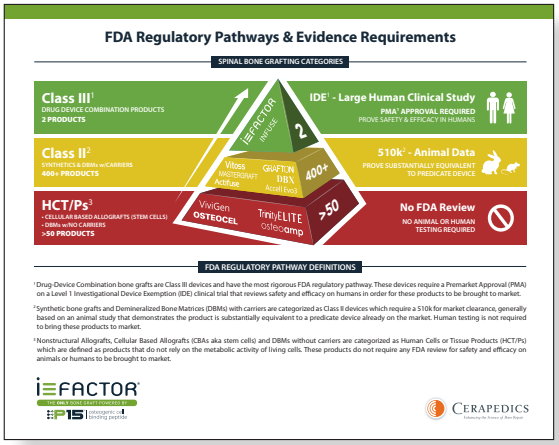
*(continued in link below)*

# SUPPORTING DOCUMENTS




Cerapedics i-FACTOR Manufacturing Video
*"How is i-FACTOR Manufactured?"*

[Click here to view the video](#)
cerapedics.com/tour




FDA Regulatory Pathways & Evidence Requirements Sell Sheet

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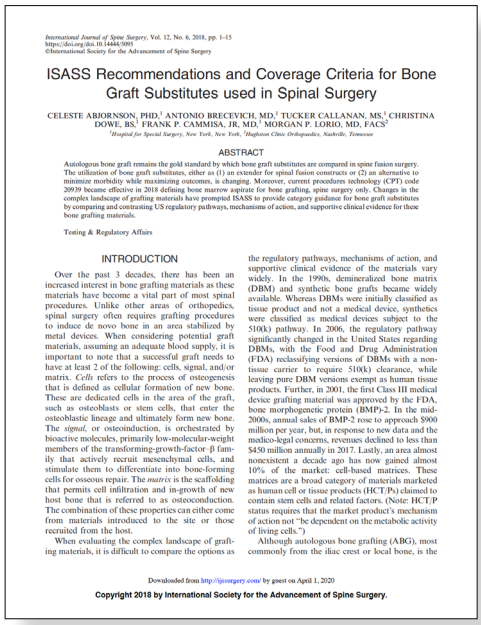

ISASS Recommendations and Coverage Criteria for Bone Graft Substitutes used in Spinal Surgery

ISASS Recommendations and Coverage Criteria for Bone Graft Substitutes used in Spinal Surgery

CELESTE ABJORNSON, PHD,[1] ANTONIO BRECEVICH, MD,[1] TUCKER CALLANAN, MS,[1] CHRISTINA DOWE, BS,[1] FRANK P. CAMMISA, JR, MD,[1] MORGAN P. LORIO, MD, FACS[2]

ABSTRACT

Autologous bone graft remains the gold standard by which bone graft substitutes are compared in spine fusion surgery. The utilization of bone graft substitutes, either as (1) an extender for spinal fusion constructs or (2) an alternative to minimize morbidity while maximizing outcomes, is changing. Moreover, current procedures technology (CPT) code 20939 became effective in 2018 defining bone marrow aspirate for bone grafting, spine surgery only. Changes in the complex landscape of grafting materials have prompted ISASS to provide category guidance for bone graft substitutes by comparing and contrasting US regulatory pathways, mechanisms of action, and supportive clinical evidence for these bone grafting materials.

Testing & Regulatory Affairs

INTRODUCTION

Over the past 3 decades, there has been an increased interest in bone grafting materials as these materials have become a vital part of most spinal procedures. Unlike other areas of orthopedics, spinal surgery often requires grafting procedures to induce de novo bone in an area stabilized by metal devices. When considering potential graft materials, assuming an adequate blood supply, it is important to note that a successful graft needs to have at least 2 of the following: cells, signal, and/or matrix. *Cells* refers to the process of osteogenesis that is defined as cellular formation of new bone. These are dedicated cells in the area of the graft, such as osteoblasts or stem cells, that enter the osteoblastic lineage and ultimately form new bone. The *signal*, or osteoinduction, is orchestrated by bioactive molecules, primarily low-molecular-weight members of the transforming-growth-factor-β family that actively recruit mesenchymal cells, and stimulate them to differentiate into bone-forming cells for osseous repair. The *matrix* is the scaffolding that permits cell infiltration and in-growth of new host bone that is referred to as osteoconduction. The combination of these properties can either come from materials introduced to the site or those recruited from the host.

When evaluating the complex landscape of grafting materials, it is difficult to compare the options as the regulatory pathways, mechanisms of action, and supportive clinical evidence of the materials vary widely. In the 1990s, demineralized bone matrix (DBM) and synthetic bone grafts became widely available. Whereas DBMs were initially classified as tissue product and not a medical device, synthetics were classified as medical devices subject to the 510(k) pathway. In 2006, the regulatory pathway significantly changed in the United States regarding DBMs, with the Food and Drug Administration (FDA) reclassifying versions of DBMs with a non-tissue carrier to require 510(k) clearance, while leaving pure DBM versions exempt as human tissue products. Further, in 2001, the first Class III medical device grafting material was approved by the FDA, bone morphogenetic protein (BMP)-2. In the mid-2000s, annual sales of BMP-2 rose to approach $900 million per year, but, in response to new data and the medico-legal concerns, revenues declined to less than $450 million annually in 2017. Lastly, an area almost nonexistent a decade ago has now gained almost 10% of the market: cell-based matrices. These matrices are a broad category of materials marketed as human cell or tissue products (HCT/Ps) claimed to contain stem cells and related factors. (Note: HCT/P status requires that the market product's mechanism of action not "be dependent on the metabolic activity of living cells.")

Although autologous bone grafting (ABG), most commonly from the iliac crest or local bone, is the

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ISASS Recommendations and Coverage Criteria for Bone Graft Substitutes used in Spinal Surgery

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i-FACTOR Story Brochure

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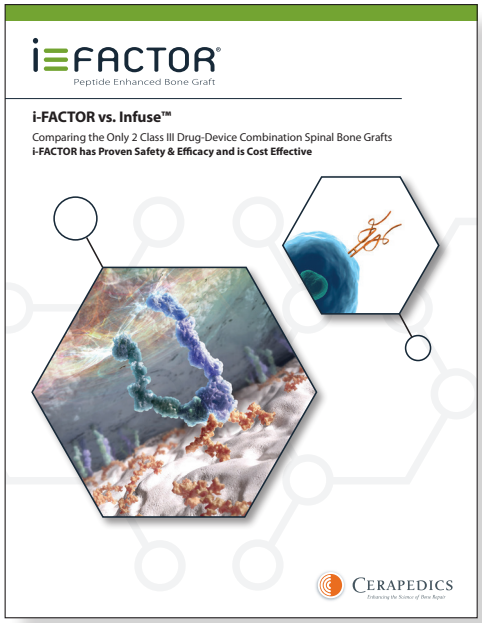
# SUPPORTING DOCUMENTS CONTINUED




i-FACTOR vs. BMP-2 (Infuse™) Brochure

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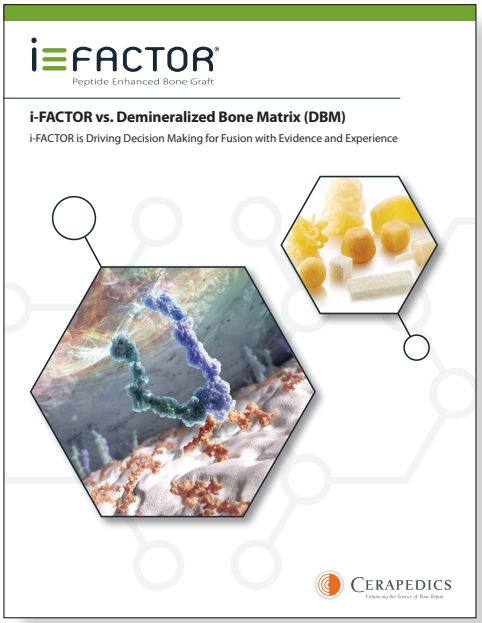


i-FACTOR vs. Demineralized Bone Matrix Brochure

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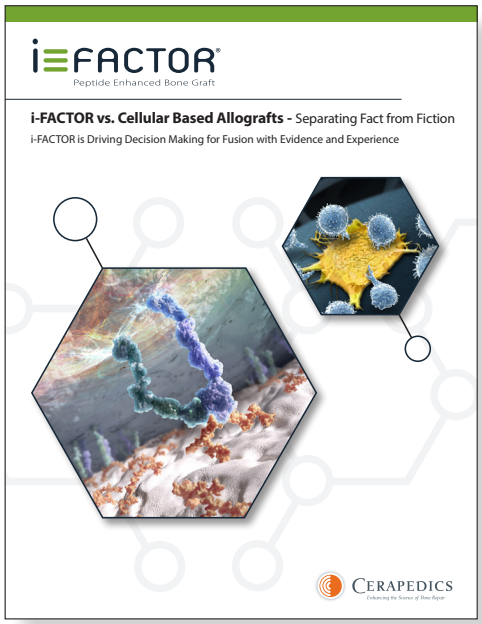


i-FACTOR vs. Cellular Based Allografts Brochure

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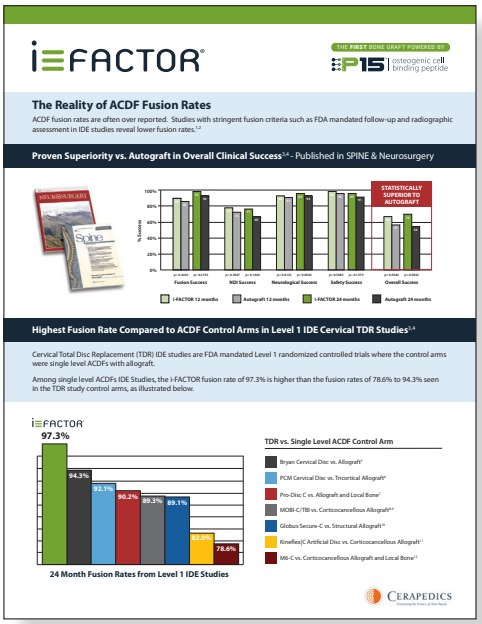
cerapedics.com/IF_vs_CBA




The Reality of ACDF Fusion Rates Sell Sheet

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