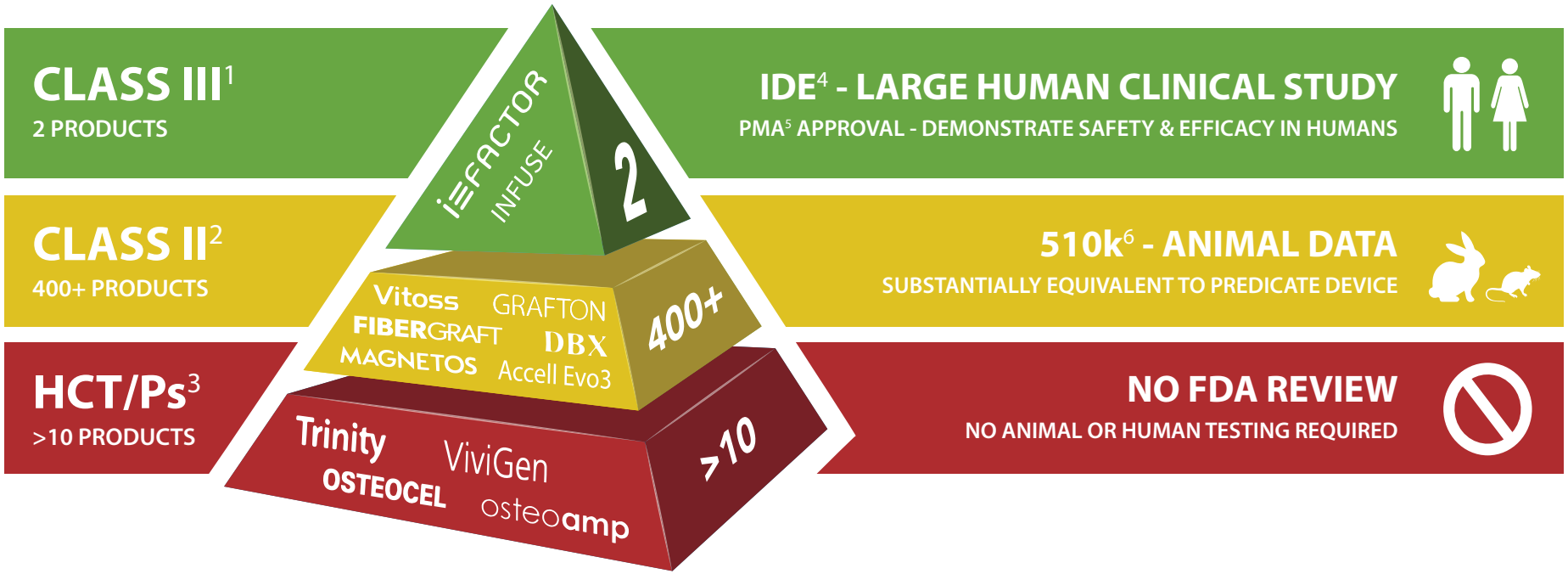
FDA Regulatory Pathways & Evidence Requirements

Bone Grafting Categories



FDA Definitions

1. **FDA Class III Drug-Device Combination:** Insufficient information exists to provide reasonable assurance of safety or effectiveness (PMA is required).
2. **FDA Class II Device:** Sufficient information to provide reasonable assurance of safety and effectiveness (510k required).
3. **HCT/P (Human Cells, Tissues and Cellular and Tissue-based products):** Minimally manipulated human tissues are not currently regulated by FDA.
4. **IDE (Investigational Device Exemption):** Allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data.
5. **PMA (Premarket approval):** Requires a clinical study under an IDE (Investigational Device Exemption) to demonstrate safety and effectiveness.
6. **510(k) [Premarket notification]:** Product is substantially equivalent to a predicate device and does not require clinical evidence of safety or efficacy.

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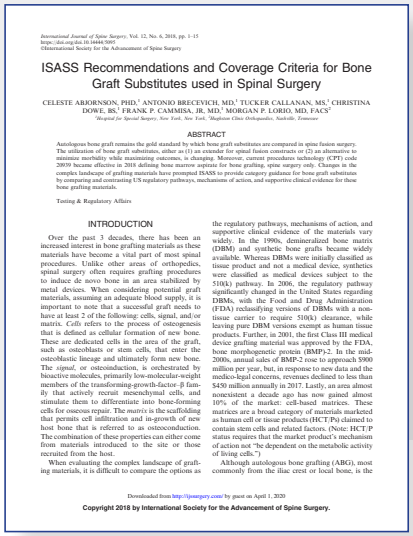
ISASS, the Largest International Spine Society, Recommends Only 2 Drug-Device Combination Spinal Bone Grafts Backed by Level 1 Human Clinical Data: i-FACTOR and Infuse[1]

*"There are only two drug-device combination products approved via the PMA process for spinal use by the FDA based on Level 1 clinical trials showing them to be safe and effective as autograft replacements. These two spine products are **Infuse** and **i-FACTOR**."*



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

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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

Table 1. Safety and efficacy of bone graft substitutes.

Category	Regulatory Pathway	Mechanism of Action	Available Data
Nonstructural allografts	HCT/P	Osteoconduction: matrix	No premarket data review by FDA. Long-standing clinical experience, reasonable body of literature
Demineralized bone grafts	510(k) as autograft extender in PLF	Osteoconduction, theoretical osteoinduction: matrix, signals?	Animal study for 510(k) clearance, limited clinical studies
Cellular-based allografts	HCT/P*	Osteoconduction, theoretical osteoinduction: matrix, signals?	No premarket data review by FDA, very limited preclinical and clinical studies
Synthetic bone grafts	510(k) as autograft extender in PLF	Osteoconduction: matrix	Animal study for 510(k) clearance, limited clinical studies
Autologous cellular grafts	510(k) for the concentration devices	Osteogenesis: cells	In vitro data for 510(k), limited clinical studies
Class III, drug-device combination products	IDE/PMA as stand-alone autograft replacements	BMP-2 osteoinductivity P-15 cellular attachment and activation	Level I IDE human clinical study required for PMA approval.

Abbreviations: HCT/P, human cell or tissue product; FDA, Food and Drug Administration; PLF, posterolateral fusion; IDE, investigational device exemption; PMA, premarket approval; BMP, bone morphogenetic protein.
*HCT/P status requires that the market product's mechanism of action not "be dependent on the metabolic activity of living cells."

i-FACTOR **PARALLELS** to Infuse

Drug and Carrier
Both are Class III Drug-Device Combination products

Advanced Biologics
Both enhance cell migration, proliferation and differentiation to bone forming cells[2,3,4,5]

Level 1 Human Clinical Trials
Both have PMA Approvals based on IDE Studies

Autograft Replacements
Both are autograft replacements, not extenders like most Synthetics & DBMs

i-FACTOR **DIFFERENCES** to Infuse

Safety Profile
i-FACTOR has no evidence of ectopic bone formation[6]

Cost
On average, i-FACTOR is 30% less expensive than Infuse[6]

Active Ingredients
i-FACTOR has P-15 Osteogenic Cell Binding Peptide

Indications
i-FACTOR's ACDF indication is based on FDA IDE Study Design protocols

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i-FACTOR® Peptide Enhanced Bone Graft

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