Chapter

Class III Spine Grafts

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Abstract

This chapter is focused on the USFDA regulation and the related efficacy evidence of bone graft materials, especially Class III drug-device combination products for use in the spine. Nonstructural allograft and cellular allograft products that do not rely on the metabolic activity of living cells are HCT/P products, which require no premarket review for safety and efficacy. Synthetic bone grafts and demineralized bone matrices (DBMs) fall under Class II and require a 510(k) for market clearance, generally on the basis of an animal study. Drug-device combination bone grafts are Class III and require an investigational device exemption (IDE) clinical trial followed by a premarket approval (PMA) application with the FDA to review safety and effectiveness. Currently, there are only two PMA-supported Class III drug-device bone graft substitutes with Level I data that demonstrate equivalence to autograft for safety and effectiveness in spine: Infuse® (rhBMP-2) and i-FACTOR (P-15 peptide). Both of these products have been shown to be effective autograft replacement options, vs. the other technologies, which are autograft extenders. The OP-1 Implant (rhBMP-7) was marketed for a period of time, but it has been removed from the market. This chapter will discuss these products along with their supporting clinical data.

Keywords: spine, bone graft, regulatory approval, clinical evidence, BMP, P-15, infuse

1. Introduction

The ideal bone graft substitute for spinal fusion would have the safety and effectiveness of autograft when used by itself, be supported by quality published clinical evidence, and be available at a reasonable cost. Most of the options available today fall short of these goals. The number and variety of bone grafting products available to choose from is extensive, totaling more than 400 at the current time. The claims about the function and value of these products are confusing, even to those with the time and expertise to evaluate them in-depth. The preclinical and clinical evidence available for making a clinical use decision is also enormously varied and subject to misinterpretation. A large reason for these challenges is that the regulatory pathways and required evidence leading to FDA approval for spinal bone graft substitutes vary widely.

Nonstructural allograft and cellular allograft products, which do not rely on the metabolic activity of living cells, are considered to be HCT/P products under the United States Code of Federal Regulations Title 21—part 1271 (HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS). Section 361 describes products that are minimally manipulated, are for homologous use only, do not have a systemic effect, and are not dependent on the metabolic activity of living cells for their primary function, in addition to other qualifications. Once a manufacturer determines a product meets all of these requirements and follows the appropriate regulations, the manufacturer can place the product on the market by simply notifying the FDA of the intent to do so. There is no premarket review by FDA for safety or effectiveness of such products. Therefore, there are no requirements for preclinical or clinical data. Since most HCT/P products have little to no peer-reviewed human clinical data, the surgeons must extrapolate the likely benefits in their clinical use.

Synthetic bone grafts and demineralized bone matrices (DBMs) fall under Class II under Section 510(k) of the Federal Food, Drug and Cosmetic Act. Section 510(k) describes a regulatory process for the clearance of products that have been demonstrated to the FDA's satisfaction to be "substantially equivalent" in safety and effectiveness to another lawfully marketed device when used for the same purpose. Market clearance requires the filing and review of a 510(k) application and a subsequent FDA review. This review is generally based on a single animal study and bench-top testing comparing the subject device with a predicate. Once again, since most 510(k) cleared products have little to no peer-reviewed human clinical data, surgeons must extrapolate the likely benefits in their clinical use.

Drug-device combination bone grafts are Class III and require an investigational device exemption (IDE) clinical trial followed by a premarket approval (PMA) application. The IDE study requirements include strict oversight from the FDA from statistical and protocol design through clinical follow-up, data integrity and analysis. These IDE studies must be prospective, controlled, blinded and statistically-powered prior to the onset. Moreover, the FDA-required outcomes for approval must be stipulated in the clinical design protocol. The review of both the IDE and PMA filings for drug-device combination products involve both the device (CDRH) and drug (CDER) branches of the FDA. The result of this rigorous process is the highest quality Level I human clinical data available. Surgeons may rely upon this data to make clinical use decisions.

2. Infuse bone graft: bone morphogenetic protein (BMP)

2.1 Bone morphogenetic protein: BMP

In 1965, Dr. Marshall R. Urist showed that demineralized bone matrix (DBM) could induce bone formation when implanted under the skin or intramuscular [1]. Urist pioneered the theory that a substance naturally present in bone was responsible for the osteoinductive bone healing activity of DBM (now Class II). He named this substance, the bone inductive principle, bone morphogenetic protein (BMP) and initiated an extensive and difficult search for these active protein molecules [2]. More than two decades later, advances in molecular biology by Dr. John Wozney's research team at the Genetic Institute described the first isolated extraction and recombinant form of BMP-2 in 1988 [3, 4]. BMP-2 and BMP-7 have been shown to have the most bone forming potential out of the 15 BMPs identified and studied to date [5]. The recombinant protein available commercially today is a synthetic, genetically engineered version of the natural protein.

BMPs are potent bone forming agents in bone regeneration and bone repair activity and are members of the TGF-Beta superfamily of cytokines. BMPs drive mesenchymal stem cells (MSCs) into osteoblastic lineage. These active protein dimeric molecules are osteoinductive and generally require a collagen sponge or ceramic carrier to enhance their handling characteristics. BMPs initiate endochondral bone formation, presumably by stimulating local MSCs and augmenting bone collagen synthesis. The BMP-2 ligand acts as a rigid clamp connecting type I and type II BMP receptor chains (BMPRs) together for transactivation. This activation causes intracellular signaling by phosphorylation of downstream signaling molecules (Smads). Smads ultimately mediate and regulate the transcription of target genes by binding to specific DNA sequences (BMP-responsive elements) [6].

2.1.1 rhBMP-2 pre-clinical

The next direction of rhBMP-2 research was to attempt to define proper dosing of the potent protein and to determine if this dosage would be specific to site or to carrier/scaffold. Formative work in this inquiry was performed in two different models by Sandhu et al. [7, 8]

The investigators first attempted to characterize the dose-response relationship of rhBMP-2 in a canine intertransverse spine fusion model. They compared increasing logarithmic rhBMP-2 doses (58, 115, 230, 460, and 920 mg) on a porous polylactic acid polymer carrier. Successful fusions postoperatively at 3 months were shown throughout this dosing range. A prior study done by this same research team demonstrated superiority of a 2300 mg rhBMP-2 dose to autologous iliac crest bone graft (ICBG) using this same technique. Quality differences above a threshold dose were not reflected in the mechanical, radiographic, or histologic features in the canine intertransverse spine fusion model from a 40-fold variation in rhBMP-2 dose [7].

Learning from the canine work, the investigators continued their work in an ovine lumbar interbody fusion model in conjunction with a cylindrical fenestrated titanium interbody fusion cage (INTER FIX, Medtronic Sofomor Danek, Inc., Memphis, TN). The cage was filled with rhBMP-2-collagen or ICBG (control). The sheep all appeared radiographically fused at 6 months. However, the histologic evaluation revealed that 33% (2/6) of the control group were fused as compared with 100% (6/6) of the rhBMP-2 group ($P < 0.001$). The scar involving the control group was 16-fold more than that seen with the rhBMP-2 group ($P < 0.01$) [8].

A rhesus monkey nonhuman primate model with rhBMP-2 on a collagen carrier within a titanium cage (Sofomor Danek, Memphis, TN) was the subsequent evolutionary step from the ovine model [9]. As optimal dosing for rhesus monkeys had not been previously established, three concentrations of rhBMP-2 [0.00 mg/mL sham (buffer only), 0.75 mg/mL low dose, or 1.50 mg/mL high dose) were tested. The results demonstrated that both the investigational rhBMP-2 groups achieved arthrodesis at 6 months histologically as compared to the sham group. As before with the ovine model, the blinded nonhuman primate model radiographic assessment was suboptimal but the sagittal CT assessment was consistent with the histology. The higher dose rhBMP-2 (1.5 mg/mL) caused faster and denser bone formation; this study established the dose used in the upcoming US IDE trial.

Fusion environments differ. A cage environment places the contained collagen carrier under protected direct compression forces between large vascularized opposing bony vertebral endplate surfaces. Posterolateral fusion presents a difficult environment with limited surface area and an intertransverse process fusion gap under distraction forces. Moreover, the surrounding muscle envelope applies mechanical compression on the graft material and may contribute to a pseudarthrosis or an hourglass configured fusion.

A standard compression resistant carrier with concomitant dosing concentration for rhBMP-2 was deemed necessary. Boden et al. studied a ceramic carrier [60% hydroxyapatite and 40% tricalcium phosphate (TCP)] in a nonhuman primate laminectomy model. Concentrations of rhBMP-2 (0, 6, 9, or 12 mg) were compared to ICBG. Fusion occurred with each rhBMP-2 carrier including the 0 mg/rhBMP-2 ceramic carrier alone group [10]. No significant overgrowth occurred involving the thecal sac, as bone growth induction was confined to ceramic carrier. The ceramic carrier was judged to be satisfactory for posterolateral application.

2.1.2 rhBMP-2 clinical trials

The "elimination" of the gold standard, autologous iliac crest bone graft (ICBG) harvest, in lumbar fusion was scientifically proposed by Burkus et al. in 2002 [11]. Anterior lumbar interbody fusion (ALIF) utilizing a combination of rhBMP-2 (1.50 mg/mL concentration) on an absorbable collagen sponge (ACS) carrier-filled tapered titanium fusion cage was shown to have an equivalent (~90%) radiographic (X-ray and CT) fusion rate to that of ICBG. This 2 year, multicenter, prospective, randomized, nonblinded human trial design compared an investigational Class III drug/device combination product (Infuse®, Medtronic Sofamor Danek, Memphis, Tennessee) on a Type-1 ACS (143 patients) to a control ICBG (136 patients); all 273 patients received the same tapered titanium fusion cage (LT-cage, Medtronic Sofomor Danek, Memphis, Tennessee). Osseous fusion rate was confirmed in 94.5% of the investigational group versus 88.7% of the control group at the two-year follow up. Outcomes of particular surgical interest including operative time (1.6 h), estimated blood loss (109.8 mL), adverse events from iliac crest harvest (0%), reported bone graft site discomfort (0%), and bone graft site appearance complaint (0%) were all less in the investigational group as compared to the control group at 2.0 h, 153.1 mL, 5.9, 32, and 16%, respectively. FDA approval was granted on July 2, 2002 for the rhBMP-2/ACS combination product in conjunction with the tapered titanium fusion cage (Infuse®/LT-Cage or Medtronic Sofamor Danek, Memphis, Tennessee) in the treatment of lumbar degenerative disc disease.

A traditional posterolateral spine fusion application (PLF) was the next step in the evaluation of rhBMP-2 on a ceramic granule carrier (60% hydroxyapatite and 40% TCP) in humans as a forged extrapolation of the seminal nonhuman primate work by Boden et al. [12]. Randomization of 25 patients (whose spondylolisthesis was ≤ Grade 1) into one of three groups was performed; five patients (control group) received autograft PLF with pedicle screw instrumentation, 11 patients received rhBMP-2 PLF with pedicle screw instrumentation, and 9 patients received rhBMP-2 PLF in situ only. A 20 mg rhBMP-2 dose was evenly divided in a bilateral, posterolateral application in those patients receiving rhBMP-2 on a ceramic granule carrier. Load bearing through the hardware until osseous fusion ensued was revelatory in the Oswestry scores. Oswestry scores demonstrated significant improvement in the rhBMP-2 PLF in situ only group at 6 weeks, rhBMP-2 PLF with pedicle screw instrumentation group at 3 months, and control, autograft PLF with pedicle screw instrumentation group, at 6 months. The fusion rate with the combined rhBMP-2 PLF groups (in situ only or with pedicle screw instrumentation) was 100% (20/20) and with the control, autograft PLF with pedicle screw instrumentation, however, was 40% (2/5). The radiographic fusion rate for the combined rhBMP-2 PLF groups was statistically significantly higher than for the control ($P = 0.004$).

A trauma application was then explored in a prospective, controlled, randomized multicenter clinical trial evaluation of patients with open tibial fractures. All 450 patients received intermedullary nail stabilization. Patients were randomized equally ($n = 150$), dividing them among one of three treatments: a standard of care (control group) or alternatively two different concentrations of rh-BMP [(0.75 mg/mL, total dose 6 mg) or (1.5 mg/mL, total dose 12 mg) respectively)] on ACS carrier. The control group standard of care was defined, for purposes of this study, as routine soft tissue management. The specific key measure outcome in the study was defined by the proportion of patients for whom secondary intervention was required due to delayed union or nonunion within the index postoperative year.

The 1.50 mg/mL group demonstrated a 44% reduction in the risk of failure requiring secondary intervention because of delayed union. The 1.50 mg/mL rhBMP-2 group had both significantly accelerated fracture healing and wound healing, higher osseous union rates, significantly fewer secondary interventions, less hardware failure, and less infections (Gustilo-Anderson type III associated injuries). Govender et al. further concluded that the 1.50 mg/mL rhBMP-2 concentration treatment was significantly superior care to the control, standard of care [13]. FDA approval for Infuse® (rhBMP-2 and ACS) in conjunction with an intermedullary nail for acute, open tibial fracture treatment was issued on April 30, 2004.

Between 2005 and 2009, three journal articles were published on the results of the FDA approval studies on 2-stage maxillary sinus floor augmentation [14–16]. Boyne et al. evaluated two concentrations of rhBMP-2/ACS at 0.75 and 1.50 mg/mL versus bone graft control; this pilot study was the first randomized controlled trial (RCT) demonstrating safe de novo bone induction by a recombinant human protein, rhBMP-2. Core biopsies retrieved after subsequent dental implant restoration confirmed normal bone formation in all groups; the proportion of dental implants that remained functionally loaded at 36 months was 62, 67, and 76% in the control group, 0.75 mg/mL rhBMP-2/ACS group, and 1.5 mg/mL rhBMP-2/ACS group, respectively. Triplett et al. performed a pivotal, multicenter, prospective, randomized, parallel evaluation of two treatments for a 2-stage maxillary sinus floor augmentation comparing a 1.50 mg/mL rhBMP-2/ACS group with an autograft control group; this study demonstrated no rhBMP-2 related adverse events at 6 months after dental restoration and similarly effective functional loading performance in both groups. Fiorellini et al. performed a randomized, masked, placebo-controlled, multicenter clinical trial evaluating de novo bone formation for dental implant restoration following tooth extraction using 0.75 mg/mL rhBMP-2/ACS, 1.5 mg/mL rhBMP-2/ACS, placebo control (ACS alone), or no treatment control. The 1.50 mg/mL rhBMP-2/ACS group demonstrated significantly greater (twice as great) bone augmentation compared to both controls ($P \leq 0.05$). Furthermore, bone density and histology disclosed no difference between newly induced and native bone.

A compression resistant matrix consisting of bovine collagen and Beta-tricalcium phosphate-hydroxyapatite in conjunction with rhBMP-2 was next compared to ICBG (control). A prospective, randomized, multi-center trial comparing the clinical and radiographic outcomes of an investigational optimized rhBMP-2 formulation to ICBG in one level instrumented traditional PLF in 463 patients with symptomatic degenerative disc disease (DDD) with spondylolisthesis ≤ Grade 1 [17]. Osseous fusion rate was radiographically (X-ray and CT) confirmed in 96% of the investigational group versus 89% of the control group at a 2 year follow up ($p = 0.014$). Outcomes of particular surgical interest including operative time (2.5 h), estimated blood loss (343.1 mL), reported donor site morbidity (0%), failures because of nonunion (six patients), and number requiring secondary surgeries (20 patients) were all significantly less in the investigational group as compared to the control group at 2.9 h, 448.6 mL, 60%, 18 patients ($p = 0.011$), and 36 patients ($p = 0.015$), respectively. The investigators concluded that clinical outcomes were similar between groups; they further concluded that morbidity was eliminated with the use of the optimized 2 mg/mL rhBMP-2 concentration in the compression resistant matrix. Eight patients (3.3%) with cancer (basal cell carcinoma, lung, lymphoma, ovarian, pancreatic, prostate, squamous cell carcinoma, and vocal cord) were reported in the optimized rhBMP-2 matrix group as compared to two patients (0.9%) with cancer (colon and lymphoma) in the control group. The four-fold increase in cancer in the optimized rhBMP-2 matrix group was not reported as possible device-related adverse events, as the cancer types were heterogeneous and statistically nonsignificant ($p = 0.107$). A nonapproval letter was received by

Medtronic on March 9, 2011 regarding the optimized AMPLIFY rhBMP-2 Matrix. The FDA nonapproval stemmed from the fourfold increased cancer risks in the investigational group and was linked to the high dose rhBMP-2 form of AMPLIFY versus the prior approved low dose forms.

Amidst the high-profile controversy, Yale University Open Data Access (YODA) retrieved Medtronic's safety and efficacy data on file in toto. Contract funding support of both the research and preparation of the work was provided by Medtronic to Yale. The Centre for Reviews and Dissemination (CRD) was then commissioned by the YODA initiative in an unprecedented effort by industry to facilitate unbiased review of the relevant benefits and harms of rhBMP-2 as used specifically in spinal fusion surgery; CRD has no direct financial conflict with Medtronic. Two successive publications in the Annals of Internal Medicine were issued in 2013 regarding the findings of the YODA initiative; the dissimilitude between the two publications were the extraction methods and the different studies included [18, 19]. Simmons et al. found rhBMP-2 had increased fusion rates versus ICBG, 12% higher (CI, 2–23%); Fu et al. found similar overall lumbar fusion rates between rhBMP-2 and ICBG Simmons et al. found nonsignificant increased cancer risk after rhBMP-2 (relative risk, 1.98 [CI 0.86–4.54]); Fu et al. found rhBMP-2 at 24 months had increased cancer risk (risk ratio, 3.45 [95% CI, 1.98–6.00]). Fu et al. also found rhBMP-2 to have associated increased risk for wound complications and dysphagia in off-label use in anterior cervical spine surgery, and nonsignificant increased risk for retrograde ejaculation and urogenital problems after on-label ALIF.

The data synthesis from the YODA initiative and more recent publications report mixed findings with regards to rhBMP-2 usage complications and cancer incidences after rhBMP-2 [20–23]. This same data synthesis suggests that an informed public might have benefited from earlier disclosure and blinded outcome assessment in retrospect.

3. i-FACTOR™: P-15 peptide

In the interest of developing products with greater biological specificity and a potentially better safety profile, a number of peptides (rather than proteins like BMPs) have been evaluated for their role and value in bone formation [24]. Peptides differ from proteins in size and structure, typically being much smaller molecules of between 2 and 50 amino acids compared to proteins (e.g., BMPs), which are much larger (>50 amino acids). Many of these peptide sequences are known for having numerous biochemical cellular signaling roles, especially during de novo tissue formation and in remodeling and injury response. Among the more promising peptides are those found in the cell interaction domain of the master control region of Type I collagen [25]. Type I collagen is comprised of two α1 and one β2 polypeptide chains that wrap around each other to form a right-handed triple helix, a collagen monomer. Numerous monomers polymerize to form the massive, rope-like collagen fibrils found in tissues. Type I collagen not only provides a supportive physical scaffold for cells and confers form and strength to tissues including skin, tendons and, in combination with rigid crystalline hydroxyapatite, bones, it also assumes dynamic, biological functions by regulating tissue assembly, cell differentiation, growth, regeneration, and biomineralization. Numerous functional domains and bioactive peptide sequences on a single collagen molecule are present at regular intervals across the width, and along the length of the polymeric collagen fibril. The high density of bioactive sites on collagen makes it the ideal polyvalent substrate for cells and bioactive factors.

The importance of these peptides and their functions is highlighted by the fact that they have been conserved over 65 M years of evolution as the cell interaction domain remains the same as that found in dinosaur Type I collagen [26]. This segment of the collagen molecule tends to become exposed and more bioavailable during chemical or traumatic cleavage of the collagen molecule. Among the peptides from the cell interaction domain, one referred to as P-15 was found to be 4500 times more potent for cell binding than the others. This peptide is a 15 amino acid sequence that represents a unique "kinked" tertiary protein structure on Type I collagen that facilitates its presentation to mesenchymal stem cells (MSC's) and their daughter cells along the osteoblastic lineage [27]. P-15 has been found to attract MSC to the implant by providing a favorable environment that facilitates cell attachment. The attraction is followed by a specific receptor-mediated attachment that activates down-stream molecular events via receptor-activated cascade pathways. These events activate and accelerate new bone formation as they attract, attach, and activate bone forming cells. These processes are circular and self-reinforcing once initiated. In addition, P-15 has been shown to benefit biochemical mechanisms such as proliferation, differentiation, migration, cell survival, among others.

In 1996, Qian and Bhatnagar published their first investigations on the P-15 peptide for application in bone tissues. In this paper, they showed that attaching this 15 amino acid peptide (P-15) to a calcium phosphate anorganic bone mineral (ABM) led to dramatic increases in cellular response in culture. Their work suggested that this combination might be a useful addition to the bone grafting armamentarium [28]. The in-vitro model demonstrated the ABM-bound P-15 stimulated human-derived pre-osteoblast resulting in significantly increased number of bound cells and the initiation of down-stream molecular events associated with differentiation and osteoinductive activities. Additionally, it was observed that mechanical forces on the cellular cytoskeleton may be generated by P-15 surface integrin interactions. These forces are believed to contribute to mechanotransduction with profound consequences on cellular differentiation.

Over the subsequent decades, numerous in vitro studies demonstrated that the P-15 peptide would elicit specific biological responses from bone forming lineage cells (pre-osteoblasts as well as MSC.) The stimulation/differentiation of MSC was demonstrated at both the molecular level as seen by upregulation of mRNA production, and the protein level as evidence by the cellular release of bone-regeneration associated proteins and growth factors, including alkaline phosphatase, BMP-2 and Collagen Type I [29]. The mechanism of action that elicits these effects is related to the P-15 peptide "plugging in" to surface receptors on these cells, which turns on the genetically programmed downstream cellular responses.

Qian and Bhatnagar showed that P-15 bound to ABM increases the number of bound human fibroblasts and stimulates cellular activation and spreading [28].

Liu et al. demonstrated that P-15 bound to surface increases the number of bound pre-osteoblastic cells and stimulates cellular activation [30]. The authors also noted a significant increase in specific cell surface integrin activation and focal adhesion kinase activation on surface treated with P-15 compared to control substrates, an indication of the direct biological influence of the P-15 peptide on cells.

Yang et al. demonstrated that P-15 bound to ABM stimulates upregulation of cellular BMP-2 and alkaline phosphatase production and the onset of calcification. Alkaline phosphatase production is an indicator of cellular differentiation to osteoblasts as well as their activity toward bone formation [31].

Yuan et al. found that P-15 bound to ABM stimulates early formation of mineralization nodes [32].

In vivo studies using a rabbit drill hole model demonstrated that ABM-bound P-15 significantly enhances the generation of new bone formation yielding histological evidence of mature bone tissue [33]. The P-15/ABM material yielded statistically more new bone formation at two, four and 8 weeks with over seven-times higher percentage of new bone as compared to ABM alone [33]. A sheep interbody lumbar fusion animal study demonstrated that ABM-bound P-15 yielded fusion rates equivalent to the "gold-standard" of iliac crest bone graft and displayed good trabecular bridging bone structure at 6 months [34]. Finally, rabbit intramuscular implant studies of ABM-bound P-15 established that the P-15 peptide does not support bone formation outside of a bony tissue environment. This can be interpreted as a safety factor, since ectopic bone formation in clinical use is unlikely. These effects translated from tissue culture into animal implantation, showing promise for bone grafting applications with strong bone formation in the absence of ectopic bone formation.

In 1999, the FDA granted the first of two PMA approvals for the use of the P-15 peptide for dental bone grafting to Ceramed on the basis of a prospective, randomized, Level-I IDE study demonstrating safety and effectiveness. This product, Pepgen P-15, has been used in ~500,000 patients to date in the United States.

In 2000, Cerapedics began developing the P-15 peptide technology platform, called i-FACTOR™ bone graft (P-15 Putty), for use in orthopedics and spine surgery indications. i-FACTOR bone graft is a composite bone graft consisting of the synthetic P-15 peptide (biomimetic of the Type I collagen peptide) absorbed onto ABM (naturally-derived calcium phosphate particles) and then suspended in an inert hydrogel carrier. Cerapedics received the first CE mark for i-FACTOR bone graft in 2008 for all orthopedic applications, including spine. Under the CE mark, the product has been used in >50,000 patients to date.

Cerapedics initiated an IDE trial for single level ACDF in an allograft ring in 2006, which culminated in PMA approval in 2015. This FDA-approved trial was prospective, randomized, blinded, controlled and statistically-powered, thus represents Level I study data [35]. In this 319-patient trial, i-FACTOR bone graft successfully met the predefined noninferiority criteria for radiologic fusion (88.9 vs. 85.8% for control), neck disability index (28.8 change vs. 27.4% for control), neurological success (93.7 vs. 93% for control), and safety (97.5 vs. 95.4% for control). More importantly, an FDA-mandated, prospectively designed statistical analysis of the Overall Clinical Success, defined as individual patients who were successful for all four of the primary outcomes, demonstrated statistical superiority to local autograft in overall clinical success (68.8 vs. 56.9%) at 12 months. This statistical superiority was maintained at the 24-month evaluation.

Following the introduction of the i-FACTOR bone graft in the EU, based on a CE-mark, numerous clinical evaluations were performed with i-FACTOR bone graft in the lumbar clinical indication. Mobbs et al. published a prospective ALIF study in which i-FACTOR was used as a stand-alone bone graft inside a PEEK interbody device [36]. In this study, an independent radiological evaluation found a 94% fusion rate by thin cut CT at 24 months, along with a statistical improvement in all clinical evaluations. The authors concluded that, based on their experience, "the study demonstrates a high fusion rate and clinical improvement comparable to the published results for ALIF using autograft or BMP, while avoiding the complications specific to those materials." This study represents an approved use in the EU and Australia, which would be considered off-label in the United States.

Lauweryns et al. published the results from a prospective intra-patient randomized study comparing i-FACTOR bone graft to local autograft in PLIF fusions [37]. In this study, contralateral cages were randomized to be filled with either i-FACTOR bone graft or local autograft, and fusions were assessed by thin cut CT. This study demonstrated faster fusion with i-FACTOR bone graft compared to local autograft. i-FACTOR bone graft was statistically superior with regards to percentage of patients with complete bridging fusion at both 6 months (97.7% for i-FACTOR vs. 59.1% for autograft) and 12 months (97.8% for i-FACTOR vs. 82.2% for autograft). At 24 months, the fusion rates were no longer statistically different. The authors concluded that "i-FACTOR is associated with faster formation of bridging bone when compared to autologous bone in patients undergoing PLIF." This study represents an approved use in the EU and Australia, and would be considered off-label in the United States.

In March 2018, the FDA approved an IDE for Cerapedics to initiate another IDE study. This second prospective IDE study is in single level TLIF procedures. In this study, an advanced formulation of P-15 (P-15 L bone graft) is being randomized against local autograft as the control. This study is expected to enroll 364 patients and has a 2-year endpoint for the PMA filing of Level I data.

Both the well-established mechanism of action regarding the stimulatory effects of P-15 peptide along with the extensive clinical data resulting from an IDE, Level I clinical study, strongly support the safety and effectiveness of P-15 peptide in the form of i-FACTOR bone graft.

4. The OP-1 implant: BMP-7

There is a third drug-device combination spinal bone graft product, which deserves some discussion: the OP-1 implant formerly commercialized by Stryker Biotech under FDA humanitarian device exemptions (HDE) OP-1 was bone morphogenetic protein (BMP)-7 on a collagen delivery carrier. The BMP-7 was bound to the collagen prior to packaging and terminal sterilization. Following study in long bone nonunions, the OP-1 implant was studied as an autograft replacement for primary posterolateral spinal fusion (PLF) under an IDE (IDE G990028).

After failing to meet the primary outcomes of the study to qualify for a PMA approval [rejection at the FDA advisory panel meeting in November, 2007], Stryker Biotech filed an HDE for revision PLF, which was granted in 2004. The Humanitarian Device Exemption (HDE) pathway is a method of gaining very limited FDA approval for a medical device. The device has to be intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8000 individuals in the United States per year. Although the application is similar to a premarket approval (PMA) application, the product is exempt from effectiveness requirements and, therefore, does not require a well-controlled Level I clinical trial. The application is required to only provide sufficient technical information to demonstrate that the device will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from the use of the device outweighs the risk of injury or illness from its uses.

The OP-1 device was commercialized by Stryker in the United States until 2010 and then, subsequently sold to Olympus. OP-1 was later removed from the market worldwide.

5. Conclusions

Nonstructural allograft and cellular allograft products marketed as HCT/Ps do not require any FDA review for safety or efficacy. Synthetic bone grafts and DBM's require a 510(k) for clearance on the basis of animal studies, and most of these technologies have little to no meaningful clinical data. Currently, there are only two

PMA-supported Class III drug-device bone graft substitutes available with Level I data that demonstrate equivalence in safety and effectiveness to autograft in the spine: Infuse® (rhBMP-2) and i-FACTOR bone graft (P-15 peptide). Both of these technologies have multiple peer-reviewed clinical studies that can be used to evaluate their effectiveness and make a clinical use decision.

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Conflict of interest

Jeffrey G. Marx, PhD, is a full-time employee and an officer of Cerapedics Inc.

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