Nos. A14-1149, A14-1150, A14-1151, A14-1152, A14-1153, A14-1154

State of Minnesota

In Court of Appeals

JULIE K. ANGELES, PAUL V. ANGELES, CLAUDE DAVENPORT, RUTH DAVENPORT, MICHAEL MANUEL, REBECCA MANUEL, LARRY MARSE II, TRUDY MARSE, CHARLENE MEAD, DARREL MEAD, CHARLES STAROVASNIK, JR.,

Plaintiffs-Appellants,

vs.

MEDTRONIC, INC., MEDTRONIC SOFAMOR DANEK, INC.,

Defendants-Respondents.

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INTRODUCTION

Appellants allege that they were injured by a Class-III medical device—Medtronic's Infuse Bone Graft/LT-CAGE Lumbar Tapered Fusion Device ("Infuse")—whose design and labeling were approved by the Food and Drug Administration (FDA) through the agency's Premarket Approval (PMA) process.

Two types of preemption limit the claims that can be brought against the manufacturer of a PMA-approved medical device:

First, the Medical Device Amendments (MDA) to the federal Food, Drug, and Cosmetic Act (FDCA) expressly preempt any claim that would impose a state-law requirement that is "different from, or in addition to" the federal requirements imposed through the PMA process. 21 U.S.C. §360k(a); *see Riegel v. Medtronic, Inc.*, 552 U.S. 312, 316, 323 (2008); *Lamere v. St. Jude Med., Inc.*, 827 N.W.2d 782, 792 (Minn. Ct. App. 2013). The only claim that survives express preemption under §360k(a) is a "parallel" claim based on a state-law duty that is "identical" to a specific federal requirement. *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 495 (1996).

Second, 21 U.S.C. §337(a), the FDCA's no-private-right-of-action

clause, declares that all actions to enforce the FDCA "shall be by and in the name of the United States," and thus requires that the FDCA be "enforced exclusively by the Federal Government." *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 352 (2001). Federal law therefore impliedly preempts any private claim for which the existence of the FDCA is a "critical element." *Id.* at 353; *see also Flynn v. Am. Home Prods. Corp.*, 627 N.W.2d 342, 348-49 (Minn. Ct. App. 2001).

Together, "'*Riegel* and *Buckman* create a narrow gap through which a plaintiff's state-law claim must fit if it is to escape express or implied preemption.'" *Bryant v. Medtronic, Inc.*, 623 F.3d 1200, 1204 (8th Cir. 2010). "'The plaintiff must be suing for conduct that *violates* the FDCA (or else his claim is expressly preempted by §360k(a)), but the plaintiff must not be suing *because* the conduct violates the FDCA ([because] such a claim would be impliedly preempted under *Buckman*).'" *Id.*; *Perez v. Nidek Co.*, 711 F.3d 1109, 1120 (9th Cir. 2013).

In this case, the district court—following extensive authority—correctly concluded that most of Appellants' claims do not fit through the "narrow gap" between §360k(a) and *Riegel*, on the one hand, and §337(a) and *Buckman*, on the other. As another court has explained,

Appellants' claims would "establish … requirements different from, or in addition to, federal requirements for the Infuse Device" and are therefore "the exact type of claim that is expressly preempted under §360k(a)." *Caplinger v. Medtronic, Inc.*, 921 F.Supp.2d 1206, 1221-23 (W.D. Okla. 2013), Moreover, any claim "based upon defendants' promotion and marketing of the Infuse Device for off-label uses" is "impliedly preempted under *Buckman* and §337(a)." *Id.* at 1219, 1223.

Although one would not know it from Appellants' brief—which relies on three aberrational decisions that have been repeatedly rejected as contrary to statute and precedent—the district court's preemption ruling reflects the clear weight of persuasive authority. Over the past two years, numerous courts across the country have concluded, like the court below, that claims such as those asserted by Appellants are expressly and/or impliedly preempted. *See, e.g.*, *Arvizu v. Medtronic Inc.* 2014 WL 4204933 (D. Ariz. 2014); *Arthur v. Medtronic, Inc.*, 2014 WL 3894365 (E.D. Mo. 2014); *Zaccarello v. Medtronic, Inc.*, 2014 WL 3866607 (W.D. Mo. 2014); *Scanlon v. Medtronic Sofamor Danek USA Inc.*, 2014 WL 3737501 (D. Del. 2014); *Martin v. Medtronic, Inc.*, 2014 WL 3635292 (D. Ariz. 2014); *Dunbar v. Medtronic, Inc.*, 2014 WL

3056026 (C.D. Cal. 2014); *Brady v. Medtronic, Inc.*, 2014 WL 1377830 (S.D. Fla. 2014); *Beavers-Gabriel v. Medtronic, Inc.*, 2014 WL 1396582 (D. Haw. 2014); *Blankenship v. Medtronic, Inc.*, 2014 WL 1226491 (E.D. Mo. 2014); *Schouest v. Medtronic, Inc.*, 2014 WL 1213243 (S.D. Tex. 2014); *Schuler v. Medtronic, Inc.*, 2014 WL 988516 (C.D. Cal. 2014); *Hawkins v. Medtronic, Inc.*, 2014 WL 346622 (E.D. Cal. 2014); *Ledet v. Medtronic, Inc.*, 2013 WL 6858858 (S.D. Miss. 2013); *Houston v. Medtronic, Inc.*, 957 F.Supp.2d 1166 (C.D. Cal. 2013); *Kashani-Matts v. Medtronic, Inc.*, 2013 WL 6147032 (C.D. Cal. 2013); *Dawson v. Medtronic, Inc.*, 2013 WL 4048850 (D.S.C. 2013); *Gavin v. Medtronic, Inc.*, 2013 WL 3791612 (E.D. La. 2013); *Otis-Wisher v. Fletcher Allen Health Care, Inc.*, 951 F.Supp.2d 592 (D. Vt. 2013); *Wendt v. Bernstein*, 2013 WL 3199361 (Ill. Cir. Ct. 2013); *Raborn v. Albea*, 2012 WL 6600475 (La. Civ. Dist. Ct. 2012), *aff'd*, 2014 WL 1584502 (La. Ct. App. 2014). Appellants simply ignore this overwhelming body of law. Because the district court's preemption decision is correct and consistent with the weight of persuasive authority, it should be affirmed.

The district court's decisions as to Appellants' fraud claims are also correct, and should likewise be affirmed. The court concluded that

fraud claims based on alleged affirmative misrepresentations "have the potential" to escape preemption. Add.107. Nonetheless, after careful review, it concluded that Appellants' complaints do not allege fraud with the particularity required by Rule 9.02. That conclusion is plainly correct, as Appellants fail to allege with particularity *any* purported misrepresentation by Medtronic on which their surgeons allegedly relied.

Finally, there are additional, independent reasons—raised below and/or apparent on the face of the record—why Appellants' statutory and warranty claims fail.

Accordingly, the judgments below should be affirmed.

STATEMENT OF THE CASE AND FACTS

A. Statutory And Regulatory Background

1. The PMA process generally

The MDA grants the FDA exclusive authority to regulate medical devices. Through a comprehensive "regime of detailed federal oversight" (*Riegel*, 552 U.S. at 316), Congress sought to ensure that safe and effective medical devices are readily available to treat patients who need life-saving or disability-averting care. Recognizing the "undu[e] burden[]" imposed by differing state regulation, Congress adopted a

"general prohibition on non-Federal regulation" of medical devices, in the form of an express-preemption clause. H.R. Rep. No. 94-853, at 45 (1976). That provision specifies that no State may impose "any requirement" relating to the safety or effectiveness of a medical device that "is different from, or in addition to, any requirement applicable … to the device" under federal law. 21 U.S.C. §360k(a).

Under the MDA, different types of devices receive different levels of FDA scrutiny. Devices that "support[] or sustain[] human life" or "present[] a potential unreasonable risk of … injury" are designated "Class III" devices. 21 U.S.C. §360c(a)(1)(C)(ii). Innovative Class III devices, like Infuse , "incur the FDA's strictest regulation" and must receive premarket approval from the FDA before being sold. *Buckman*, 531 U.S. at 344.

"Premarket approval is a 'rigorous' process." *Riegel*, 552 U.S. at 317 (quoting *Lohr*, 518 U.S. at 477); *Lamere*, 827 N.W.2d at 789. To obtain premarket approval, a manufacturer "must submit a detailed PMA application" that contains, among other things, "specimens of the proposed labeling for the device." *Riegel v. Medtronic, Inc.*, 451 F.3d 104, 109 (2d Cir. 2006), *aff'd*, 552 U.S. 312 (2008). The FDA closely

scrutinizes PMA applications, "'weigh[ing] any probable benefit to health from the use of the device against any probable risk of injury or illness from such use.'" *Riegel*, 552 U.S. at 318. "The FDA spends an average of 1,200 hours reviewing each application" and "grants premarket approval only if it finds there is a 'reasonable assurance' of the device's 'safety and effectiveness.'" *Id.* (quoting 21 U.S.C. §360e(d)). If the FDA decides that the device's proposed design, manufacturing method, or labeling is inadequate, it can require revisions prior to approval. *See id.* at 319.

The FDA's regulatory role does not end with approval of an initial PMA application. "Once a device has received premarket approval, the MDA forbids the manufacturer to make, without FDA permission, changes in design specifications, manufacturing processes, labeling, or any other attribute, that would affect safety or effectiveness." *Riegel*, 552 U.S. at 319 (citing 21 U.S.C. §360e(d)(6) and 21 C.F.R. §814.39(c)). A manufacturer who wishes to make such changes must submit a PMA Supplement and may not implement the proposed changes without FDA approval. *Id.* The PMA Supplement is subject to the same rigorous standards of review as an initial PMA application. *Id.*

The FDCA grants the FDA extensive and exclusive enforcement authority. Congress has specified that all actions to enforce the FDCA "shall be by and in the name of the United States." 21 U.S.C. §337(a). Although "citizens may report wrongdoing and petition the agency to take action," there is no private right of action to enforce the FDCA. *Buckman*, 531 U.S. at 349 & n.4. Under the FDCA, the FDA has the sole authority to investigate violations of the Act and "has at its disposal a variety of enforcement options that allow it to make a measured response" to any wrongdoing. *Id.* at 349. Those options include "injunctive relief, 21 U.S.C. §332, and civil penalties, 21 U.S.C. §333(f)(1)(A); seizing the device, §334(a)(2)(D); and pursuing criminal prosecutions, §333(a)." *Id.*

2. The PMA process and off-label use

The FDA's oversight of medical devices is subject to a critical and overarching limitation. Congress has prohibited the FDA from "limit[ing] or interfer[ing] with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease." 21 U.S.C. §396. Thus, while Congress established the premarket approval system to help ensure

that innovative Class III devices possess a reasonable assurance of safety and effectiveness, Congress was also adamant that the federal government not regulate the practice of medicine. Congress therefore empowered the FDA to decide whether a new device may be sold, but forbade the agency to regulate how an approved device may be used.

For this reason, the FDA has said that "[t]he term 'unapproved uses'"—a term repeatedly used by Appellants—"is … misleading," because the agency does not regulate the use of medical products. FDA, *Use of Approved Drugs for Unlabeled Indications*, 12 FDA Drug Bull. 4-5 (1982). Rather than approve or disapprove particular *uses*, the FDA approves or disapproves *devices*. 21 U.S.C. §360e(a) ("A class III *device* … is required to have[] … *approval* under this section") (emphasis added); *accord Nightingale Home Healthcare, Inc. v. Anodyne Therapy, LLC*, 2008 WL 4367554, at *6 (S.D. Ind. 2008) ("[T]he FDA does not approve or disapprove the use of medical devices for specific treatments."), *aff'd*, 589 F.3d 881 (7th Cir. 2009). Accordingly, "[o]nce the FDA has cleared a device …, physicians may use the device in any manner they determine to be best." *Cooper v. Smith & Nephew, Inc.*, 259 F.3d 194, 197 (4th Cir. 2001).

The FDA does not ignore that an approved device may—and likely will—be used in ways other those indicated on its label. To the contrary, in deciding whether to grant premarket approval, the FDA's "approval process generally contemplates that approved [devices] will be used in off-label ways." *United States v. Caronia*, 703 F.3d 149, 166 (2d Cir. 2012). This is because "off-label use is not illegal or even disfavored" but "an accepted and valuable part of the practice of medicine" (*Caplinger*, 921 F.Supp.2d at 1218 n.3) and often the prevailing "'standard of care'" (*Caronia*, 703 F.3d at 153). Thus, "'off-label' usage of medical devices … is an accepted and necessary corollary of the FDA's mission to regulate in this area without directly interfering with the practice of medicine." *Buckman*, 531 U.S. at 350.

The FDCA anticipates that the FDA will consider potential off-label uses and their associated risks when deciding whether to grant premarket approval. A manufacturer seeking premarket approval must submit all "data … relevant to an evaluation of the safety and effectiveness of the device …, *including information derived from investigations other than those proposed in the application*." 21 C.F.R. §814.20(b)(8)(2)(ii) (emphasis added); *see also* 21 U.S.C. §360e(c)(1)(A).

In turn, when determining whether to grant a PMA application, the FDA must consider not only the "conditions of use … suggested in the [proposed] labeling," but also "*other intended conditions of use*." 21 C.F.R. §860.7(b)(2) (emphasis added)[1]; *see also* 21 U.S.C. §360e(d)(1)(A)(ii); FDA Summary of Safety and Effectiveness Data: Clinical Section Checklist, at 6 (2010) (FDA considers "off-label use" "[d]uring its review"), http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHTransparency/UCM220929.pdf.

The FDA may therefore determine that the proposed labeling for a device does not adequately discourage off-label uses or warn of their risks, and may condition PMA approval on the addition or strengthening of such warnings. *See* 21 C.F.R. §814.82(a) (FDA may "condition … approval of the device" on any "requirements FDA determines are necessary to provide reasonable assurance … of the safety and effectiveness of the device," including "[p]rominent display in the labeling … of warnings, hazards, or precautions important for the device's safe and effective use").

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[1] A device's "intended use" can include "uses other than the ones for which [the manufacturer] offers it." 21 C.F.R. §801.4

Finally, if the FDA becomes concerned about off-label use after approval, it may require post-approval changes to the device. The agency may, for example, "require a manufacturer to provide additional labeling that addresses potential off-label uses." *Reeves v. AcroMed Corp.*, 44 F.3d 300, 305-06 (5th Cir. 1995) (citing 21 C.F.R. §895.25)); *accord* 21 C.F.R. §814.82; *Gomez v. St. Jude Med. Daig Div. Inc.*, 442 F.3d 919, 931 (5th Cir. 2006). The FDA also retains the power "to … remov[e] [the device] from the market" (*Gomez*, 442 F.3d at 931) if it concludes that potential off-label use renders the device too dangerous.

3. Premarket approval of Infuse

Appellants admit (Compl.¶24)[2], and FDA records confirm, that the FDA granted premarket approval to Infuse in 2002, after nearly 1½ years of scrutiny. *See* R.Add.1-2. FDA records also confirm the text of the device's FDA-approved warning label. *See* R.Add.10-25.[3]

Infuse is an implantable device comprising two components: the bone-graft component, which contains a protein capable of initiating

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[2] As there are generally no material differences between Appellants' respective original complaints, or between their respective first amended complaints, pleading citations are to the *Angeles* complaints, unless otherwise noted.

[3] These materials are judicially noticeable as official records that cannot reasonably be questioned. Minn. R. Evid. 201(b).

bone growth; and the LT-Cage component, a titanium cage into which the bone-graft component is to be placed. *See* R.Add.10; Compl.¶26. The FDA requires that the two components be "sold separately." R.Add.10.

The FDA approved and required a specific label to accompany the bone-graft component alone. *Cf.* R.Add.10 (directing reader to distinct cage-component label for cage-related information). As relevant here, that label instructs surgeons that Infuse is to "be implanted via an anterior … approach" at "one level" of the lumbar spine (R.Add.12) and that "**[t]he InFUSE Bone Graft component must not be used without the LT-CAGE.**" R.Add.18. The label, in addition to noting reports of "back and leg pain," warns that "[e]ctopic and/or exuberant bone formation," "[f]oreign body (allergic) reaction," "[i]nfection," and "nerve damage" are among the "potential adverse events which may occur with spinal fusion surgery with the InFUSE Bone Graft" component of the device. R.Add. 18-19.

Appellants concede that the FDA considered "potential off-label use" and associated risks when it granted Infuse premarket approval. Compl.¶¶33-34; Br.6-7. Recognizing that surgeons might choose to use it off-label, the FDA mandated that the Infuse label caution against

certain off-label uses (such as use of the device "without the LT-Cage" (R.Add.10 (emphasis omitted)), and warn of possible risks associated with off-label uses (such as "posterior bone formation" when the device is implanted "by a posterior lumbar interbody fusion procedure with cylindrical threaded cages" (R.Add.13)).

B. Appellants' Claims Against Medtronic

Appellants allege (Compl.¶98) that they or their spouses underwent spinal fusion surgery in which their respective surgeons used Infuse in an off-label manner, insofar as the surgeon did not implant the device via an anterior approach, implanted the device at multiple levels of the spine, and/or failed to use the device's LT-Cage component, all in contravention of the warnings required by the FDA and given by Medtronic. Appellants allege (Compl¶100) that they or their spouses suffered injuries caused by their surgeons' off-label use of Infuse, including complications from ectopic bone growth, nerve damage, infection, back and leg pain, and inflammatory reaction.

Appellants do not allege that Infuse or any of its components deviated in any respect from the design or labeling requirements imposed by the FDA through the PMA process.

C. Proceedings Below

The cases in this appeal are among hundreds of similar cases that were companioned in the district court. *See* Add.75-76. Because the complaints in the companioned cases were largely identical, the parties and the district court agreed that the court's ruling on Medtronic's motion to dismiss the first-filed case—*Lawrence*—would control all companioned cases. *See* Add.76.

The district court granted Medtronic's motion to dismiss, concluding in its extensive analysis that Appellants' non-fraud claims are expressly preempted because they would "impose different or additional requirements upon [Medtronic] under state law." Add.104. It further held that any claim based on Medtronic's alleged "illegal off-label promotion … is impliedly preempted by *Buckman* and Section 337(a)." Add.104-105.

The district court also dismissed Appellants' fraud claims. The district court held that the fraud claims are "expressly preempted under Section 360k(a)" insofar as they rely on alleged omissions by Medtronic regarding the safety and effectiveness of the Infuse device, because such claims are, in effect, failure-to-warn claims that would impermissibly

"impose different or additional requirements upon Defendants under state law." Add.107. The district court held, however, that fraud claims premised upon allegations that Medtronic "affirmatively misled" Appellants' surgeons by "provid[ing]" false information "have the potential to escape … preemption." Add.107.

The court nonetheless dismissed Appellants' fraud claims "for failure to plead with the requisite particularity" demanded by Rule 9.02. Add.109. The court found that Appellants' complaints "do not … identify what representations were made to them or their physicians and allegedly relied on by them in deciding to go ahead with the surgical procedure at issue." Add.109. The court noted, "for example," that although Appellants "have alleged that [Medtronic] paid consulting fees to various physicians who published favorable studies about their use of the Infuse device, … [Appellants] have identified no statements in any of those studies that were allegedly false or misleading and that were relied upon by [Appellants] or their physicians." Add.109-110.

Pursuant to the companioning orders, the decision in *Lawrence* dismissed with prejudice all of the claims in the companioned cases except fraud claims based on alleged affirmative misrepresentations,

which were dismissed without prejudice. *See* Add.75-76.[4]

Following the *Lawrence* decision, Appellants and other plaintiffs in the companioned cases filed amended complaints in an attempt to plead fraud with sufficient particularity. The district court has issued detailed opinions evaluating ten of these amended complaints, denying Medtronic's motion to dismiss in four cases, and granting its motion in the six cases now on appeal.

In dismissing Appellants' fraud claims, the district court held that "even under the arguably more permissive pleading standard of *Martens* [*v. Minnesota Mining & Manufacturing Co.*, 616 N.W.2d 732 (Minn. 2000)], the allegations of the Amended Complaint[s] fall short of Minnesota fraud pleading standards." Add.9. The court found that insofar as the claims rely on alleged misrepresentations in the medical literature, each Appellant's allegations are insufficient because they fail to "identify a specific article or articles containing alleged misrepresentations that [Appellant's surgeons] read and relied on in

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[4] The sufficiency of Appellants' non-fraud and fraud-by-omission claims must be judged therefore according to their *original* complaints, not their amended complaints. *See In re Hennepin Cnty. 1986 Recycling Bond Litig.*, 540 N.W.2d 494, 497 (Minn. 1995). Nevertheless, Appellants repeatedly rely on their amended complaints to bolster the claims dismissed with prejudice by *Lawrence*. *See* Br.6, 11-14.

deciding to perform an off-label procedure in [Appellant's] case." Add.87. To the extent Appellants' claims rest on alleged misrepresentations purportedly made at medical conferences, the court found the allegations insufficient because Appellants identify no specific statements, "have not named any of the alleged speakers in question, and … have not identified the date, or even the year of the conference[s]" at which the alleged misrepresentations were purportedly made. Add.9. Finally, the court found Appellants' claims based on alleged misrepresentations by sales representatives inadequately pleaded because Appellants do "not identify any statements made by" a sales representative, and fail to allege that their respective surgeons "relied on anything said by a [sales] representative in deciding to use the Infuse device in an off-label procedure." Add.70.

STANDARD OF REVIEW

Dismissal under Rule 12.02(e) is reviewed *de novo*. *Mahoney & Hagberg v. Newgard*, 729 N.W.2d 302, 306 (Minn. 2007). A claim preempted by federal law must be dismissed. *Leonard v. Nw. Airlines, Inc.*, 605 N.W.2d 425, 428 (Minn. Ct. App. 2000).

ARGUMENT

I. APPELLANTS' NON-FRAUD AND FRAUD-BY-OMISSION CLAIMS ARE PREEMPTED.

The MDA's express-preemption clause, 21 U.S.C. §360k(a), forbids States from maintaining any safety or effectiveness requirement that is "different from, or in addition to" those imposed by the FDA. Seeking to ensure "that innovations in medical device technology are not stifled by unnecessary restrictions," and recognizing the "undu[e] burden[]" on device manufacturers when "differing requirements … are imposed by jurisdictions other than the Federal government," Congress enacted §360k(a) as a "general prohibition on non-Federal regulation" of medical devices. H.R. Rep. No. 94-853, at 12, 45. The MDA thus "swept back some state obligations and imposed a regime of detailed federal oversight," enforced by an expert federal agency rather than by private plaintiffs and lay juries applying state tort law. *Riegel*, 552 U.S. at 316.[5]

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[5] The Supreme Court has twice rejected the argument that a presumption against preemption applies in the medical-device context. In *Riegel*, the Court rejected the dissent's reliance on such a presumption because "the text of [§360k(a)]" plainly evinced Congress's intent to displace "the tort law of 50 States." 552 U.S. at 326; *see also id.* at 316 (Congress intended to "swe[ep] back some state obligations" and replace them with "a regime of detailed federal oversight."); *cf. id.* at 334 (Ginsburg, J., dissenting). And in *Buckman*, the Court held that there is "no presumption against pre-emption" for state-law claims

In addition, 21 U.S.C. §337(a), the FDCA's no-private-right-of-action clause, impliedly preempts any private action to enforce the FDCA. Congress granted the FDA exclusive authority to enforce the medical-device regulations and gave it "complete discretion" to decide "how and when [its enforcement tools] should be exercised." *Heckler v. Chaney*, 470 U.S. 821, 835 (1985). The Supreme Court has recognized that "this authority is used … to achieve a somewhat delicate balance of statutory objectives," a balance that "can be skewed" if private tort suits are allowed. *Buckman*, 531 U.S. at 348. Thus, while "citizens may report wrongdoing and petition the agency to take action" (*id.* at 349), §337(a) forbids private claims that cannot be established without reliance on the FDCA and thus amount to private enforcement of its provisions.

Although Congress's preemption of state tort claims may leave some individuals who are injured by FDA-approved medical devices "'without … judicial recourse,'" the loss to those comparatively few individuals was, in Congress's estimation, outweighed by the benefit to the far greater number "who would suffer without new medical devices

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seeking to enforce FDCA requirements. 531 U.S. at 347-48.

if juries were allowed to apply the tort law of 50 States to all innovations." *Riegel*, 552 U.S. at 326. As an alternative to private tort suits, Congress granted the FDA substantial authority to police device manufacturers under federal law. *See Buckman*, 531 U.S. at 349.[6]

Appellants should not be allowed to circumvent Congress's carefully crafted regulatory scheme. Congress recognized that state tort litigation can impair public health by inhibiting the development of life-saving medical treatment. In deciding to "swe[ep] back some state obligations and impose[] a regime of detailed federal oversight" (*Riegel*, 552 U.S. at 316), to be enforced by an expert federal agency rather than lay juries, Congress further recognized that tort suits are ill-suited for regulating complex medical devices. In particular, Congress was concerned that "[a] jury … sees only the cost of a more dangerous design, and is not concerned with its benefits," because "the patients who reaped those benefits are not represented in court." *Id.* at 325.

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[6] Appellants are wrong to equate preemption with "immunity." Br. 3. Although many private tort claims are barred, the government may bring civil and criminal charges against a manufacturer who violates the FDCA. *See Buckman*, 531 U.S. at 349; *Flynn*, 627 N.W.2d at 349. Moreover, a person injured by a PMA-approved device may still sue the manufacturer, notwithstanding §360k(a), if the manufacturer failed to adhere to the device's PMA requirements—*e.g.*, by failing to provide the FDA-mandated warnings—and that failure caused the person's injuries.

Congress's determination that medical devices should be regulated by an expert federal agency, rather than through individual tort verdicts issued by lay juries across 50 states, must be respected.

Appellants' efforts to evade §360k(a) on the one hand, and §337(a) on the other hand, are without merit.

A. Appellants' Non-Fraud And Fraud-By-Omission Claims Are Expressly Preempted.

1. Appellants' claims are subject to §360k(a).

Appellants recognize (*cf.* Br.17) that under §360k(a) the imposition of federal requirements on a medical device preempts any state-law requirements "different from, or in addition to," the federal requirements. Appellants—who do not deny that the Infuse device received premarket approval—also acknowledge that "for purposes of express preemption analysis under §360k(a), '[p]remarket approval … imposes requirements' applicable to the approved device." Br.18 (quoting *Riegel*, 552 U.S. at 322).

Nevertheless, Appellants argue that §360k(a) does not apply to their claims, either because the FDA's grant of premarket approval purportedly "established federal requirements only for the Infuse/LT-Cage combination device, not for Infuse Protein used alone or with

another implant," or because "the PMA process only established federal requirements for the device when marketed for use for the purposes set forth in its labeling." Br.18. But each of these theories has been correctly rejected by almost every court to have considered them.

a. The FDA approves devices, not uses.

Contrary to Appellants' assertion that "FDA approval of the Infuse/LT-Cage combination device was limited to a particular form of spinal surgery" (Br.5), the FDA approved the device as such, without limitation. As explained above (*supra* pp.8-9), the FDA may not interfere with the practice of medicine, and thus approves only devices—their design, manufacture, and labeling—not how devices may be used.

b. Preemption applies regardless how an approved device is used.

By its plain terms, §360k(a) applies whenever the FDA has established "any requirement applicable … *to the device*." 21 U.S.C. §360k(a)(1) (emphasis added). Accordingly, application of §360k(a) depends only on whether the FDA has imposed requirements on the device, not on the use to which the device is subsequently put. That is as it must be, because the FDA does not regulate how approved devices

are used, a decision committed to doctors' professional judgment. *See* 21 U.S.C. §396.

In fact, the vast majority of courts have held that preemption under §360k(a) applies irrespective of how a device is used:

> [U]nder §360k(a)(1), the question is not whether there are federal requirements applicable to a particular *use* of a device; the question is whether there are federal requirements applicable "to the *device*." If there are—and, as *Riegel* makes clear, the PMA process unquestionably imposes such requirements—then any state requirements that are different from, or in addition to, those federal requirements are preempted. Nothing in the statute suggests that the preemption analysis somehow depends on how the device is used.

Riley v. Cordis Corp., 625 F.Supp.2d 769, 779 (D. Minn. 2009); *accord Hawkins*, 2014 WL 346622, at *6; *Houston*, 957 F.Supp.2d at 1176; *Ledet*, 2013 WL 6858858, at *3; *Gavin*, 2013 WL 3791612, at *11 *Caplinger*, 921 F.Supp.2d at 1218.

Ignoring this authority, Appellants rely (Br.19-20) on *McDonald-Lerner v. Neurocare Associates, P.A.*, 2013 WL 7394926 (Md. Cir. Ct. 2013). But *McDonald-Lerner's* conclusion "that preemption is inapplicable" to "off-label use" is contrary to the statutory text and "clearly inconsistent with *Riegel*, which also involved the off-label use of

a medical device." *Gavin*, 2013 WL 3791612, at *12; *see also* Add.99.[7] *Riegel* applied §360k(a)—and held the plaintiff's claims preempted—despite the doctor's off-label use of the device at issue. If §360k(a) did not apply to off-label uses, as *McDonald-Lerner* holds, then the claims in *Riegel* would not have been preempted. But the Supreme Court held that they were. *See Hawkins*, 2014 WL 346622, at *6 (under *Riegel*, off-label use "does not summarily preclude a finding of express preemption"). *McDonald-Lerner* is, therefore, not persuasive.[8]

c. Premarket approval imposes preemptive federal requirements on all components of a device.

Courts are nearly unanimous that, as held by the district court (Add.100), premarket approval extends to all components of an approved device, even when a physician uses the components separately. Thus, almost every court to consider this issue in an Infuse

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[7] In *Riegel*, the label stated that the catheter at issue was not to be used in patients with diffuse or calcified stenoses and not to be inflated above 8 atmospheres, but was used in a patient with diffuse and calcified stenoses and inflated to 10 atmospheres.

[8] Although also wrongly decided (*see infra* pp.27-30), even *Ramirez v. Medtronic Inc.*, 961 F.Supp.2d 977 (D. Ariz. 2013), on which Appellants rely, recognizes that requirements imposed through the PMA process "are not 'use-specific'" and "do not purport to apply only to approved uses of Infuse." *Id.* at 987-88.

case has held that "premarket approval is as controlling of the individual components … as it is to the device as a whole." *Hawkins*, 2014 WL 346622, at *5; *accord, e.g.*, *Beavers-Gabriel*, 2014 WL 1396582, at *8; *Ledet*, 2013 WL 6858858, at *3; *Houston*, 957 F.Supp.2d at 1176; *Gavin*, 2013 WL 3791612, at *11-12. Courts addressing other devices have likewise held that claims arising from use of a particular component of a device are "also subject to PMA preemption." *Smith v. Depuy Orthopaedics Inc.*, 552 F.App'x 192, 196 (3d Cir. 2014); *accord, e.g.*, *Bertini v. Smith & Nephew, Inc.*, 2014 WL 1028950, at *2-6 (E.D.N.Y. 2014); *Gross v. Stryker Corp.*, 858 F.Supp.2d 466, 487 (W.D. Pa. 2012); *Riley*, 625 F.Supp.2d at 780.

Consequently, there is no merit to Appellants' assertion that premarket approval of the Infuse device "does not establish federal requirements applicable to either one of the components of the device used separately." Br.19. On the contrary, "[u]se of the Infuse Bone Graft Component without the LT-Cage is simply an off-label use of the device." *Hawkins*, 2014 WL 346622, at *5.[9]

[9] In support of their contention that "FDA approval of [the Infuse device] was expressly restricted to the use of both components together" (Br.19), Appellants quote the bone-graft component's labeling, which

d. Alleged off-label promotion does not negate premarket approval.

Appellants are wrong when they contend that "[t]he PMA only established federal requirements for the Infuse/LT-Cage device when marketed for use in accordance with its labeling." Br.20. In support of this contention, Appellants rely principally (Br.21-22) on *Ramirez*, which erroneously holds that §360k(a) does not apply to claims arising from alleged off-label promotion because, supposedly, "[t]he shield [of preemption] drops when the manufacturer violates federal law." 961 F.Supp.2d at 993.[10]

First, even if a manufacturer has violated federal law, the PMA for the device remains in place, and §360k(a) continues to preempt any state-law claim that would impose requirements "different from, or in addition to" those imposed by federal law.[11] *See, e.g.*, *Talbott, v. C.R.*

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instructs surgeons that the device is to be used only with the LT-Cage. But Appellants conflate the scope of premarket approval, which applies to the device as such, and the warnings that the FDA required accompany the device. The warnings are guidance to physicians, not limits on the scope of premarket approval.

[10] Appellants also rely (Br. 22) on *Hornbeck v. Medtronic, Inc.*, 2014 WL 2510817 (N.D. Ill. 2014), which is wrongly decided for the same reasons as *Ramirez*.

[11] Any suggestion that a federal violation automatically negates

Bard, Inc., 63 F.3d 25, 28 (1st Cir. 1995) (preemption applies as long as the FDA has not revoked PMA, even when the FDA has determined that the manufacturer violated federal law).

Second, preemption under §360k(a) does not turn on how a device is promoted. By its plain terms, §360k(a) applies whenever the federal government has established "any requirement applicable … to the device." Indeed, "nothing in §360k(a) suggests that the preemption analysis somehow depends on how the device is being promoted to be used." *Caplinger*, 921 F.Supp.2d at 1218; *accord, e.g.*, *Scanlon*, 2014 WL 3737501, at *5; *Hawkins*, 2014 WL 346622, at *6; *Gavin*, 2013 WL 3791612, at *11; *Ledet*, 2013 WL 6858858, at *3; *see also Perez*, 711 F.3d at 1111-13, 1117-19 (§360k(a) preempts fraud-by-omission claim despite off-label marketing allegation); *Bertini*, 2014 WL 1028950, at *6 (§360k(a) preempts claims notwithstanding allegation manufacturer marketed device for use with component not indicated on its FDA-approved label).

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premarket approval and thus obviates the preemptive effect of §360(k) is contrary to the FDCA. Revocation of premarket approval requires explicit FDA action. *See, e.g.*, 21 U.S.C. §§360e(e)(1)-(2), (g)(2); 21 C.F.R. §§814.46(c), 16.62, 16.80, 16.95(b)(2).

Nor could any rule conditioning preemption on how a device is promoted be reconciled with the statute as interpreted in *Riegel*. If application of §360k(a) turned on how a device is promoted, then claims arising from one doctor's unilateral decision to use an approved device in an off-label manner would be subject to §360k(a), but claims arising from another doctor's decision to make the *same* use of the *same* device would *not* be subject to §360k(a) if that doctor was induced to do so by off-label promotion. That cannot be correct, because application of §360k(a) depends on "whether the Federal Government has established requirements applicable to [the device]." *Riegel*, 552 U.S. at 321. For any given device at any given time, the federal government either has established requirements or it has not. Thus, any suggestion that allegations of off-label promotion render §360k(a) inapplicable "is inconsistent with the text of §360k(a)." *Gavin*, 2013 WL 3791612, at *11.

Ramirez is to the contrary, but "*Ramirez* has been rejected—for good reason—by numerous courts." *Beavers-Gabriel*, 2014 WL 1396582, at *10. Indeed, "the majority of other courts … have rejected *Ramirez*." *Martin*, 2014 WL 3635292, at *6. This is because "the *Ramirez* holding

is not consistent with the text of §360k(a) [or] the scope of federal requirements imposed on Class III devices." *Houston v. Medtronic, Inc.*, 2014 WL 1364455, at *5 (C.D. Cal. 2014). *Ramirez*'s roundly discredited approach should be rejected here as well.

e. The Infuse device is subject to preemptive device-specific requirements.

Assuming that which must (yet cannot) be proven, Appellants argue that "the general federal regulatory requirements applicable to this case do not satisfy the first step of the *Riegel* test because they are not device-specific." Br.22. But Infuse (and each of its components) *is* subject to device-specific requirements—namely, the requirements imposed by the FDA when it granted premarket approval to the device. *See Riegel*, 552 U.S. at 322. Those preemptive requirements—which dictate, *inter alia*, the device's design and labeling—remain in force as long as the device is marketed. Thus, there is no basis for Appellants' assertion that "Medtronic's post-PMA conduct is governed by FDA regulations 'reflect[ing] entirely generic concerns about device regulation generally,' not federal requirements specific to the Infuse/LT-

Cage device." Br. 24 (quoting *Riegel*, 552 U.S. at 322).[12]

2. Appellants' non-fraud and fraud-by-omission claims are preempted by §360k(a).

Appellants' non-fraud and fraud-by-omission claims are expressly preempted by §360k(a). Appellants do not allege that Medtronic failed to provide any warnings required by the FDA; nor do they allege that the design of the Infuse device was anything other than that approved by the FDA. Instead, Appellants contend that Medtronic was, as a matter of state law, required to give *additional* warnings about risks purportedly associated with off-label use, or to employ a *different* design. *See, e.g.*, *Ledet*, 2013 WL 6858858, at *4; *Kashani-Matts*, 2013 WL 6147032, at *4. But because any such duty would impose state-law requirements "different from, or in addition to" the federal

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[12] Quoting a brief filed by the current Solicitor General, Appellants suggest that §360k(a) should apply only when the FDA has imposed device-specific requirements "'on the same subject'" as a plaintiff's claim. Br.23. But the Solicitor General admits that this position—which is contrary to the statutory text—conflicts with *every* appellate decision in "every case since *Riegel*." Brief of the United States as *Amicus Curiae*, at 15-16, *Medtronic, Inc. v. Stengel*, 2014 WL 211719, *cert. denied*, 134 S.Ct. 2839 (2014). But even if the law were as the Solicitor General wished, it would not help Appellants, because the FDA *has* imposed device-specific requirements on the Infuse device with respect to off-label uses, which is the precise subject of their claims. *See supra* pp.13-14.

requirements imposed by the FDA through the PMA process, Appellants' claims are—as the district court held (Add.107)—barred by §360k(a). *See, e.g.*, *Bryant*, 623 F.3d at 1205-06; *McMullen v. Medtronic, Inc.*, 421 F.3d 482, 490 (7th Cir. 2005).

There is a narrow exception to express preemption for claims that "'parallel,' rather than add to, federal requirements." *Riegel*, 552 U.S. at 330 (quoting *Lohr*, 518 U.S. at 495). But to be "parallel," a claim must rest on the violation of a state-law requirement that is "identical" to an existing federal requirement. *Lohr*, 518 U.S. at 495; *accord McMullen*, 421 F.3d at 489 (requirements must be "'*genuinely* equivalent'"); *Lamere*, 827 N.W.2d at 790 (requirements must be "'substantially identical'").

Establishing liability through a parallel claim is therefore "more difficult than it would be in a typical product liability case." *White v. Stryker Corp.*, 818 F.Supp.2d 1032, 1037 (W.D. Ky. 2011). To state a "parallel" claim, each Appellant must allege (1) the violation of a specific federal requirement applicable to the Infuse device; (2) the violation of an *identical* state-law duty; and (3) that the predicate federal violation caused Appellant's injuries. *See, e.g.*, *Wolicki-Gables v.*

Arrow Int'l, Inc., 634 F.3d 1296, 1300-01 (11th Cir. 2011); *McMullen*, 421 F.3d at 488-89; *Caplinger*, 921 F.Supp.2d at 1214; *White*, 818 F.Supp.2d at 1039-40.[13]

Citing *Bausch v. Stryker Corp.*, 630 F.3d 546 (7th Cir. 2010), Appellants insist that while "manufacturers who comply with federal laws may be entitled to preemption, … those who violate federal law" are not. Br.36 (emphasis omitted). But it is not the law, and *Bausch* did not hold, that the presence of *any* alleged federal violation allows *any* state-law claim to avoid preemption. On the contrary, the Supreme Court has held that "although [§360k(a)] can be read to allow certain state-law causes of action that parallel federal safety requirements, it does not and cannot stand for the proposition that *any* violation of the

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[13] Appellants rely (Br.24) on *Alton v. Medtronic, Inc.*, 970 F.Supp.2d 1069 (D. Or. 2013), which erroneously suggests that "*Lohr* and its progeny contemplate two types of 'parallel' state-law claims"—claims predicated on identical federal and state duties, and claims "premised on conduct that contravenes state-law duties of such generality as not to present any risk of interference with the federal medical-device regulatory scheme." 970 F.Supp.2d at 1097. The purported second type of parallel claim does not exist. *Riegel rejected* the contention that general state-law duties escape preemption under §360k(a): "[n]othing in the statutory text suggests that the pre-empted state requirement must apply *only* to the relevant device, or only to medical devices and not to all products and all actions in general." 552 U.S. at 328; *see also Lamere*, 827 N.W.2d at 791-92 ("[g]eneral tort duties ... 'directly regulate' the device itself" and are therefore preempted).

FDCA will support a state-law claim." *Buckman*, 531 U.S. at 353 (emphasis added). Instead, as *Bausch* acknowledges, state requirements escape preemption under §360k(a) only if "*the plaintiff can show that the requirements are 'genuinely equivalent'*" to a federal requirement. 630 F.3d at 552 (emphasis added); *see also Wolicki-Gables*, 634 F.3d at 1300; *McMullen*, 421 F.3d at 489; *Lamere*, 827 N.W.2d at 790. Unlike Appellants' claims, the claim in *Bausch* was deemed to be a parallel claim because the plaintiff's state-law *manufacturing*-defect claim rested on the alleged violation of federal *manufacturing* requirements. *See* 630 F.3d at 558-59. As the district court correctly held, and as Medtronic explains below, Appellants' non-fraud and fraud-by-omission claims do not present any such parallelism.

a. Appellants' failure-to-warn claims are expressly preempted.

Appellants "make no claim that Defendants violated the labeling requirements imposed by the premarket approval for the Infuse device." Add.104. Therefore, Appellants' failure-to-warn claims must rest on the proposition that, to comply with state law, Medtronic had to give warnings different from or in addition to those required by the FDA

when it granted premarket approval to the Infuse device.[14] But any claim based on a state-law requirement that Medtronic provide different or additional warnings runs headlong into §360k(a). As the Supreme Court has explained, §360k(a) "[s]urely … would pre-empt a jury determination that the FDA-approved labeling for a [device] violated a state common-law requirement for additional warnings." *Riegel*, 552 U.S. at 329; *accord Wolicki-Gables*, 634 F.3d at 1301-02; *Bryant*, 623 F.3d at 1205; *McMullen*, 421 F.3d at 489-90.

It is irrelevant that the different or additional warnings purportedly required by state law concern off-label use. Like the court below, the overwhelming majority of courts to have considered such claims have held them to be preempted. *See, e.g.*, *Beavers-Gabriel*, 2014 WL 1396582, at *13-14; *Blankenship*, 2014 WL 1226491 at *6; *Schouest*,

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[14] Appellants' failure-to-warn claims include their "claims for negligence, negligence per se, strict liability, the [violation of] Minnesota statut[e] …, and unjust enrichment." Br.27 n.24. Appellants' fraud-by-omission claims also are failure-to-warn claims preempted by §360k(a). *See Schouest*, 2014 WL 1213243, at *5 ("the key dividing line" for preemption purposes "is between claims alleging affirmative misrepresentations and those alleging that Medtronic should have done more"); *see also Perez*, 711 F.3d at 1118 ("fraud by omission claim is expressly preempted by §360k(a)"); *Littlebear v. Advanced Bionics, LLC*, 896 F.Supp.2d 1085, 1091 (N.D. Okla. 2012) ("fraud by nondisclosure is expressly preempted").

2014 WL 1213243, at *9-10; *Houston*, 957 F.Supp.2d at 1177; *Caplinger*, 921 F.Supp.2d at 1221-23.

Appellants argue that their failure-to-warn claims escape preemption because "once Medtronic began to promote the Infuse Protein for intended uses that had not been approved by the FDA, federal law required it to revise its labeling to warn of risks associated with these uses." Br.28. Appellants' argument, however, rests on a false premise. Federal law does not require—and generally forbids—manufactures of medical devices with premarket approval to make unilateral labeling changes. *See Riegel*, 552 U.S. at 319 (citing 21 U.S.C. §360e(d)(6) and 21 C.F.R. §814.39(c)). At most, federal law required Medtronic to submit a PMA Supplement seeking FDA approval for labeling changes. *Cf.* 21 C.F.R. §814.39(c).[15] But a federal requirement

[15] Although federal law *permits* manufacturers to provisionally change labels under certain circumstances (*see* 21 C.F.R. §814.39(d); *cf.* Br.28 n.25), it does not *require* them to do so. Accordingly, any state-law requirement to do so would be preempted under §360k(a). *See In re Medtronic Sprint Fidelis Lead Prods. Liab. State Court Litig.*, 2009 WL 3417867, at *17 (Minn. Dist. Ct. 2009) (Reilly, J.) ("a failure-to-warn claim cannot parallel §814.39(d) because §814.39(d) merely *permits* a device manufacturer to make a temporary change to a label whereas a successful failure-to-warn claim would *require* such a change") (quoting *Riley*, 625 F.Supp.2d at 783); *accord McMullen*, 421 F.3d at 489 (§360k(a) prevents States from requiring an act that federal law

to submit an application, which the FDA might or might not approve, is not parallel to a state-law requirement that Medtronic actually give additional warnings. As the Supreme Court has observed, "[s]tate law demand[s] a safer label; it d[oes] not instruct the Manufacturers to communicate with the FDA about the possibility of a safer label." *PLIVA, Inc. v. Mensing*, 131 S.Ct. 2567, 2578 (2011). Because the state-law duty and the federal requirement are not "'substantially identical'" (*Lamere*, 827 N.W.2d at 790), Appellants' failure-to-warn claims are preempted by §360k(a).[16]

"permits, but does not require"); *cf. Nat'l Meat Ass'n v. Harris*, 132 S. Ct. 965, 970-71 (2012) (preemption of state-law requirements "different from, or in addition to" federal requirements precludes state-law requirements that transform a "may" into a "must").

[16] Appellants' reliance (Br.27) on *Stengel v. Medtronic, Inc.*, 704 F.3d 1224 (9th Cir. 2013) (en banc), is misplaced. The failure-to-warn claim at issue there rested on an alleged violation of 21 C.F.R. §803.50, which requires manufacturers to notify the FDA of certain adverse events, a requirement that the court deemed parallel to a purported Arizona duty to provide "warning[s] to a third party." 704 F.3d at 1233. Notably, the concurring majority recognized that "any attempt"—such as that by Appellants here—"to predicate [a failure-to-warn] claim on an alleged state law duty to warn doctors directly would have been expressly preempted under 21 U.S.C. §360k." *Id.* at 1234 (Watford, J., concurring). Moreover, insofar as it allowed a claim based on an alleged failure to report adverse events to the FDA, *Stengel* is contrary to this Court's decision in *Flynn* (*cf.* 627 N.W.2d at 349*)* and the Eighth Circuit's decision in *Bryant* (*cf.* 623 F.3d at 1205-06).

b. Appellants' design-defect claims are expressly preempted.

Appellants' design-defect claims are also preempted by §360k(a).[17] Appellants do not allege that the design of the Infuse device they received was anything other than the design approved by the FDA through the PMA process. Thus, to prevail on their state-law design-defect claims, Appellants would have to prove that the Infuse device should have employed a design *different* from that approved by the FDA. *Riegel* forecloses any such claim. *See* 552 U.S. at 320 (§360k(a) preempts "claims of strict liability … and negligence in the design" of a device). Indeed, as recognized by the court below (Add.105), a state-law claim that would require a device to have a design different from that approved by the FDA through the PMA process is a frontal "attack[] on the risk/benefit analysis that led the FDA to approve" the device. *Bryant*, 623 F.3d at 1206; *accord Kemp v. Medtronic, Inc.*, 231 F.3d 216, 219 (6th Cir. 2000) (affirming dismissal of "strict products liability claims for defective design ... as well as ... claims for negligent design"). Therefore, as held by the district court (and almost all other courts

[17] Appellants' design-defect claims include their "claims for negligence, negligence per se, strict liability, and breach of express and implied warranty." Br.28 n.26.

considering Infuse-related claims), "this is precisely the type of claim that is expressly preempted" under §360k(a). Add.105; *accord, e.g.*, *Beavers-Gabriel*, 2014 WL 1396582, at *13-14; *Blankenship*, 2014 WL 1226491 at *6; *Schouest*, 2014 WL 1213243, at *9-12; *Houston*, 957 F.Supp.2d at 1176; *Caplinger*, 921 F.Supp.2d at 1222.

Appellants' argument to the contrary is without merit. Appellants argue that their design-defect claims avoid express preemption because they "allege[] that Medtronic affirmatively promoted the Infuse Protein as safe and effective for use in … off-label procedures." Br.29. But even if it exists, a federal duty to refrain from off-label promotion is not "'substantially identical'" (*Lohr*, 518 U.S. at 497; *Lamere*, 827 N.W.2d at 790) to a state-law duty to not employ a defective design. Thus, Appellants' design-defect claims are not parallel claims, even on Appellants' theory, and were correctly dismissed as preempted.[18]

c. Appellants' express-warranty claims are expressly preempted.

Appellants allege that Medtronic "expressly … warranted" that

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[18] Rather than contend that their design-defect claims are parallel claims that avoid express preemption under §360k(a), Appellants rely on discredited cases erroneously holding that §360k(a) does not apply to claims arising from alleged off-label use or promotion. *See* Br. 29-30 (citing *Ramirez*, *Hornbeck*, and *McDonald-Lerner*); *cf. supra* pp.23-30.

"off-label uses" of the Infuse device were "safe and effective," but supposedly breached that purported warranty inasmuch as "off-label uses" supposedly "were not effective, safe, and proper." Compl.¶¶128-130. As the district court—like other courts to consider identical claims—correctly recognized, this "claim would require a jury to find that the Infuse device was *not* safe and effective" as labeled. Add.106 (emphasis added); *accord Gavin*, 2013 WL 3791612, at *15-16; *Caplinger*, 921 F.Supp.2d at 1222. But that would conflict with the FDA's conclusive determination in granting premarket approval that "there is a 'reasonable assurance' of the device's 'safety and effectiveness.'" *Riegel*, 552 U.S. at 318. That the purported warranty allegedly encompassed off-label uses is immaterial. When the FDA determined that Infuse is safe and effective as labeled, it knew that medical devices often are—and that Infuse likely would be—used in an off-label manner. *See supra* pp., 10-14. The warranty claims are therefore preempted. *See, e.g.*, *Gavin*, 2013 WL 3791612, at *15 (warranty claims involving off-label use of Infuse are preempted because they would require finding "the Device was not safe and effective, … contrary to the FDA's approval"); *accord Caplinger*, 921

F.Supp.2d at 1222; *Wendt*, 2013 WL 3199361, at *1.[19]

3. Allegations of off-label promotion do not support a parallel claim.

Appellants' complaints are largely devoted to alleging that Medtronic promoted Infuse for uses not indicated on the device's label. *See* Compl.¶¶24-97. Allegations of "off-label promotion," however, "do not somehow turn" otherwise preempted "claims into 'parallel' claims that are not preempted." *Caplinger*, 921 F.Supp.2d at 1218 n.4; *accord, e.g.*, *Scanlon*, 2014 WL 3737501, at *5.

a. Growing precedent holds that federal law does not prohibit off-label promotion.

Although this Court need not reach the issue—because Appellants' claims are subject to §360k(a), and thus expressly preempted, even if federal law did prohibit off-label promotion (*see supra* 27-30)—growing precedent holds that federal law does *not* prohibit off-label promotion. According to Appellants (Br.8), a medical device promoted for off-label uses is "'deemed misbranded'" in violation of 21 U.S.C. §352(f). But, as the Second Circuit recently held, "[w]hile

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[19] *See also Gomez*, 442 F.3d at 932; *Williams v. Cyberonics, Inc.*, 388 F.App'x 169, 171 (3d Cir. 2010); *Smith v. Depuy Orthopaedics, Inc.*, 2013 WL 1108555, at *10 (D.N.J. 2013), *aff'd,* 552 F. App'x 192 (3d Cir. 2014).

the FDCA makes it a crime to misbrand," federal law "do[es] not expressly prohibit"—and cannot be construed to prohibit—"off-label promotion." *Caronia*, 703 F.3d at 160; *see also id.* at 154, 162, 168-9; *accord Schuler*, 2014 WL 988516, at *1; *Dawson*, 2013 WL 4048850, at *6; *Underwood v. Rhone-Poulenc Rorer Pharm., Inc.*, 890 So.2d 429, 430-31 (Fla. Dist. Ct. App. 2004).[20] As the FDA has explained, off-label promotion "is not itself a prohibited act under the FDCA, nor is it an element of any prohibited act." U.S. Gov't Br. at 51, *Caronia*, 703 F.3d

[20] Medtronic anticipates Appellants arguing that *Caronia* is inapplicable, both because they allege that Medtronic's purported off-label promotion was misleading rather than truthful, and because *Caronia*'s construction of the FDCA was rendered in a criminal case under the principle of constitutional avoidance. But there is no merit to either suggestion, because 21 U.S.C. §352(f)—the "misbranding" provision that, in conjunction with 21 U.S.C. §331(a), purportedly prohibits off-label promotion—does not differentiate between true and false statements. A statutory construction adopted to avoid constitutional concerns with respect to one category of conduct (such as the making of truthful statements) applies with respect to all other categories (such as the making of misleading statements) where, as here, "the statutory text provides for no distinction" between the categories, because "[t]o give the same words a different meaning for each category would be to invent a statute rather than interpret one." *Clark v. Martinez*, 543 U.S. 371, 378-79 (2005); *accord Leocal v. Ashcroft*, 543 U.S. 1, 11 n.8 (2004) (courts "must interpret [a] statute consistently, whether [they] encounter its application in a criminal or noncriminal context").

149, 2010 WL 6351497.[21] "Instead, the promotion of off-label uses plays" only "an *evidentiary* role in determining whether a [device] is misbranded." *Id*. Absent a federal requirement that manufacturers abstain from off-label promotion, Appellants cannot state a claim based on off-label promotion "that is not preempted." *Schuler*, 2014 WL 988516, at *1; *accord Dawson*, 2013 WL 4048850, at *6.

b. State law does not prohibit off-label promotion.

Even if federal law did prohibit off-label promotion, Appellants could not state a parallel claim because there is no Minnesota state-law duty to abstain from off-label promotion. That is because "even the concept of 'off-label use' is a creature of the FDCA, is defined by the FDCA, and is not a part of [state] substantive law." *Caplinger*, 921

[21] In support of their assertion that federal law prohibits off-label promotion, Appellants cite (Br.9) *Ortho Pharm. Corp. v. Cosprophar, Inc.*, 32 F.3d 690 (2d Cir. 1994), *a* Second Circuit case that predates both *Caronia* and *Sorrell v. IMS Health, Inc.*, 131 S. Ct. 2653 (2011)), the intervening Supreme Court decision on which *Caronia* relies. Appellants also cite (Br.9-10) *United States v. Caputo*, 288 F.Supp.2d 912 (N.D. Ill. 2003). But when the Seventh Circuit reviewed that decision, it *refused* to adopt the position Appellants urge. *See United States v. Caputo*, 517 F.3d 935, 940 (7th Cir. 2008) ("we need not decide today whether a seller of … medical devices has a … right to promote off-label uses"). Nevertheless, Medtronic acknowledges that whether federal law prohibits off-label promotion remains a disputed question. *Cf., e.g.*, *Houston*, 957 F.Supp.2d at 1179.

F.Supp.2d at 1219-20, 1224; *accord Gavin*, 2013 WL 3791612, at *17; *In re Zyprexa Prods. Liab. Litig.*, 2008 WL 398378, at *5 (E.D.N.Y. 2008). Therefore, even courts that have assumed that federal law prohibits off-label promotion have held that state-law claims predicated on off-label promotion are expressly preempted by §360k(a). *See, e.g.*, *Beavers-Gabriel*, 2014 WL 1396582, at *13-14; *Blankenship*, 2014 WL 1226491, at *6; *Schouest*, 2014 WL 1213243, at *9-12; *Houston*, 957 F.Supp.2d at 1177-78; *Hawkins*, 2014 WL 346622, at *10-11; *Caplinger*, 921 F.Supp.2d at 1218 n.4; *Raborn*, 2012 WL 6600475.

Unable to identify a state-law prohibition on off-label promotion, Appellants instead rely (Br.27) on the common-law duty to warn. But allegations that a manufacturer violated federal law by promoting off-label use and allegations that it violated state law by failing to issue certain warnings are not "parallel." The state-law duty Appellants invoke is a duty to provide warnings—*i.e.*, *to make statements*—about risks allegedly associated with off-label use of Infuse, but the purported federal duty that Appellants invoke is a duty *to abstain from making statements* about off-label uses of Infuse. The two duties "are not genuinely equivalent." *Coleman v. Medtronic, Inc.*, 167 Cal.Rptr.3d 300,

314 (Ct. App. 2014)[22]; *accord Hawkins*, 2014 WL 346622, at *15 ("An affirmative duty to *provide* adequate warnings is not genuinely equivalent to a federal requirement to *refrain* from a particular type of promotion.").[23]

A manufacturer therefore could fulfill the purported federal

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[22] Although *Coleman*, the sole appellate decision to allow tort claims predicated on alleged off-label promotion, correctly held that a failure-to-warn claim based on "a theory of off-label promotion" is "expressly preempted under section 360k" because "the federal and state requirements are not genuinely equivalent" (167 Cal.Rptr.3d at 313-14), it erroneously held—in acknowledged conflict with other courts—that the plaintiff could pursue a claim for off-label promotion on a negligence-*per-se* theory (*id.* at 314-16). But that is contrary to 21 U.S.C. §337(a), which requires that the FDCA be "enforced exclusively by the Federal Government" rather than by private plaintiffs (*Buckman*, 531 U.S. at 352), and a host of cases holding that negligence-*per-se* claims predicated on alleged violations of the FDCA are impliedly preempted. *See infra* p.56.

[23] Appellants' reliance (Br.35) on *Riley* and on *Cornett v. Johnson & Johnson*, 48 A.3d 1041, 1057 (N.J. 2012), is misplaced. In dictum, the *Riley* court speculated about whether it might be "possible" for a failure-to-warn claim coupled with an off-label-promotion allegation to escape preemption, but expressly declined to reach the issue. 625 F.Supp.2d at 783. Most courts to reach the issue have relied on *Riley* to conclude that allegations of off-label promotion do *not* save state-law claims from preemption. *See, e.g.*, *Dawson*, 2013 WL 4048850, at *6; *Gavin*, 2013 WL 3791612, at *11; *Caplinger*, 921 F.Supp.2d at 1218 & n.4. And *Cornett*'s sole authority for allowing a failure-to-warn claim to proceed based on allegations of off-label promotion was the very dictum in *Riley* that reserved rather than resolved the issue. Not surprisingly, therefore, *Cornett* is at odds with other cases to consider the issue. *See, e.g.*, *Otis-Wisher*, 951 F. Supp.2d at 599 (declining to follow *Cornett*).

requirement without satisfying the state-law requirement: If the manufacturer fails to provide warnings about foreseeable off-label uses but does not promote such uses, it could violate the state-law duty to warn while complying with any federal requirement to abstain from off-label promotion. Thus, as the *Caplinger* court held in dismissing virtually identical claims:

> [O]ff-label promotion allegations do not somehow turn plaintiff's claims into "parallel" claims that are not preempted. … [T]he federal requirement that manufacturers not promote devices for off-label uses is not genuinely equivalent to the state law requirements that a manufacturer provide adequate warnings …. It is possible to violate the state law requirement while complying with the federal requirement and vice versa.

921 F.Supp.2d at 1218 n.4. That is critical because "[s]tate and federal requirements are not genuinely equivalent"—and thus are not parallel for purposes of §360k(a)—if, as here, "a manufacturer could be held liable under the state law without having violated the federal law." *McMullen*, 421 F.3d at 488-89; *Wolicki-Gables*, 634 F.3d at 1300.

B. Appellants' Claims Are Impliedly Preempted.

Congress not only declined to create a private cause of action under the FDCA, but affirmatively required that any action to enforce the FDCA "be by and in the name of the United States." 21 U.S.C.

§337(a). This provision requires that the FDCA be "enforced exclusively by the Federal Government"—not by private plaintiffs. *Buckman*, 531 U.S. at 352.

Moreover, Congress granted the FDA "complete discretion" in deciding "how and when [its enforcement tools] should be exercised." *Heckler*, 470 U.S. at 835. That discretion is necessary "to achieve a somewhat delicate balance of statutory objectives," which "can be skewed" if private tort suits are allowed. *Buckman*, 531 U.S. at 348; *see also id.* at 349 ("This flexibility is a critical component of the statutory and regulatory framework under which the FDA pursues difficult (and often competing) objectives."). Thus, "[t]he FDCA leaves no doubt that it is the Federal Government rather than private litigants who are authorized to file suit for noncompliance with the medical device provisions." *Id.* at 349 n.4.

As *Riley* explains, §337(a) forbids private plaintiffs from asserting any "state claim [that] would not exist if the FDCA did not exist," or any claim for which "'the existence of [the] federal enactments is a critical element,'" because such a claim "is in substance (even if not in form) a claim for violating the FDCA" and may be enforced only by the federal

government. 625 F.Supp.2d at 777, 790 (quoting *Buckman*, 531 U.S. at 353). Moreover, it is not enough that a claim be based on a "traditional state law cause[] of action." Br.33. Rather, the specific "'*conduct* on which the claim is premised must be the type of *conduct* that would traditionally give rise to liability under state law.'" *Blankenship*, 2014 WL 1226491, at *3 (emphasis added) (quoting *Caplinger*, 921 F.Supp.2d at 1214); *accord Pinsonneault v. St. Jude Medical, Inc.*, 953 F.Supp.2d 1006, 1017 (D. Minn. 2013).

1. Claims predicated on off-label promotion are impliedly preempted.

Any claim predicated on alleged off-label promotion is impliedly preempted. There is no traditional state-law duty to abstain from off-label promotion. Indeed, the very *concept* of off-label promotion—which did not and could not exist until Congress required manufacturers to obtain FDA approval of devices and their labels—"is a creature of the FDCA, is defined by the FDCA, and is not a part of [state] substantive law." *Caplinger*, 921 F.Supp.2d at 1219-20, 1224; *see also supra* pp.43-44 (citing additional cases).

Claims predicated on off-label promotion are therefore "impliedly preempted under *Buckman* and §337(a)" (*Caplinger*, 921 F.Supp.2d at

1219), "because promoting the off-label use of an FDA-approved medical device is not unlawful under 'traditional state tort law which[] had predated the federal enactments in question'" (*Dawson*, 2013 WL 4048850, at *6 (quoting *Buckman*, 531 U.S. at 353)), and claims based on such conduct "exist," if at all, "solely by virtue of the FDCA." *Buckman*, 531 U.S. at 353; *accord, e.g.*, *Blankenship*, 2014 WL 1226491, at *8-9; *Ledet*, 2013 WL 6858858, at *5; *Houston*, 957 F.Supp.2d at 1178. Such claims are barred by §337(a) because they would "usurp the FDA's regulatory oversight role for policing purported violations of" the FDCA. *Dawson*, 2013 WL 4048850, at *7. This Court should therefore reject Appellants' attempt to enforce a purported federal restriction on off-label promotion as intruding on the FDA's "complete discretion … to decide how and when" to enforce its regulations. *Heckler*, 470 U.S. at 835.[24]

[24] As relevant here, the FDA seeks to "regulat[e] the marketing and distribution of medical devices without intruding upon decisions statutorily committed to the discretion of health care professionals." *Buckman*, 531 U.S. at 350. Recognizing that "off-label uses … may be important therapeutic options and may even constitute a medically recognized standard of care," the FDA—notwithstanding its view that off-label promotion might sometimes constitute evidence of misbranding—has, in the exercise of its discretion pursuant to §337(a), adopted a nuanced approach to the regulation of off-label promotion,

Observing that *Buckman* described the claim before the Court as a fraud-on-the-FDA claim, Appellants argue that *Buckman* is "inapposite" here because they are suing for "Medtronic's tortious conduct against them." Br.32. But that is a false distinction: the plaintiffs in *Buckman* "sought damages from [the manufacturer] under state tort law" for "injuries resulting from the use of" an allegedly unsafe device. 531 U.S. at 343. Thus, Appellants' claims, which seek damages under state tort law for injuries allegedly caused by Infuse, are not materially distinguishable from those held preempted in *Buckman*.

Just as in *Buckman*, moreover, Appellants' claims would interfere with the FDA's "difficult task of regulating the marketing and distribution of medical devices without intruding upon decisions

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and expressly endorsed a manufacturer's dissemination of off-label information in certain circumstances. FDA, *Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices* 2 (2011), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM285145.pdf. A private action to enforce a purported prohibition on off-label promotion would therefore interfere with the agency's exercise of its statutorily mandated discretion. Allowing Appellants' claims to proceed would be particularly inappropriate here, where the Government took no action after a multiyear investigation of Medtronic's alleged conduct. *See* Medtronic, Inc., Form 8-K (May 16, 2012), http://www.sec.gov/Archives/edgar/data/64670/000119312512236814/d355299d8k.htm.

statutorily committed to the discretion of health care professionals." *Buckman*, 531 U.S. at 350. As in *Buckman*, Appellants' claims could "discourage[]" manufacturers "from seeking … approval of devices with potentially beneficial off-label uses for fear that such use might expose the manufacturer … to unpredictable civil liability," and thus could "deter off-label use despite the fact that the FDCA expressly disclaims any intent to directly regulate the practice of medicine, … and even though off-label use is generally accepted." *Id.* at 350-51 (citing 21 U.S.C. §396). Indeed, because off-label use often constitutes the standard of care for some patients (*see, e.g.*, 12 FDA Drug Bull. at 5), allowing private suits predicated on the promotion of such uses will ultimately harm patients by "inhibit[ing], to the public's detriment, informed and intelligent treatment decisions." *Caronia*, 703 F.3d at 166.

2. Appellants' design-defect and failure-to-warn claims are impliedly preempted.

However construed, Appellants' design-defect and failure-to-warn claims are impliedly preempted.[25]

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[25] Appellants' contention (Br.35) that claims which survive express preemption cannot be impliedly preempted is contrary to *Buckman*, which holds that "an express pre-emption provision" does *not* "bar[] the ordinary working of conflict pre-emption principles." 531 U.S. at 352

If Appellants contend that state law required Medtronic to change Infuse's design or labeling without FDA approval, their claims are impliedly preempted, because federal law affirmatively prohibits manufacturers from changing the design or labeling of PMA-approved devices without obtaining prior or ultimate FDA approval. *See* 21 C.F.R. §814.39; *Riegel*, 552 U.S. at 319. Any claim predicated on the contention that Medtronic was required to unilaterally adopt a different design or label must therefore fail, because, "[u]nder the Supremacy Clause, state laws that require a private party to violate federal law are pre-empted." *Mut. Pharm. Co. v. Bartlett*, 133 S. Ct. 2466, 2470 (2013).

Appellants' claims are also impliedly preempted if, instead, Appellants contend that Medtronic had a duty to submit a PMA Supplement to the FDA seeking authorization to modify Infuse's design or label. First, any duty to submit a PMA Supplement "exist[s] solely by virtue of the FDCA" and thus may be enforced only by "the Federal Government rather than private litigants." *Buckman*, 531 U.S. at 349

(quotation marks omitted). Similarly, Appellants insinuation (Br.33 n.28) that the combination of implied and express preemption eliminates all possible claims against medical device manufacturers is false. A private plaintiff may sue a manufacturer when injured because a device did not conform to its PMA requirements.

n.4, 353. Accordingly, any claim based on that duty is preempted under *Buckman*, which holds that "federal … medical device laws pre-empt[] a state tort-law claim based on [a manufacturer's] failure to properly communicate with the FDA." *Mensing*, 131 S.Ct. at 2578. Second, the mere submission of a PMA Supplement would not have resulted in the modification of Infuse's design or warning label, as purportedly demanded by state law; any such change would have been dependent on the FDA's approval of the application. *Riegel*, 552 U.S. at 319 (citing 21 U.S.C. §360e(d)(6) and 21 C.F.R. §814.39(c)). But any state-law claim is impliedly preempted unless the defendant "could *independently* do under federal law what state law requires of it." *Mensing*, 131 S.Ct. at 2579 (emphasis added). The possibility that "the Federal Government *might*" have approved a design or labeling change if Medtronic had submitted a PMA Supplement does not "suffice to prevent federal and state law from conflicting for Supremacy Clause purposes." *Id.* Allowing the imposition of state-law liability based on "conjectures" about what the FDA would have done if a PMA Supplement had been submitted would "render[] … pre-emption all but meaningless" and deprive "the Supremacy Clause [of] any force." *Id.*

3. Appellants' warranty claims are impliedly preempted.

Appellants argue that express-warranty claims are never preempted by §360k(a) because express warranties, unlike implied warranties, "'arise from the representations of the parties'" rather than by operation of "state law." Br.30.[26] But that argument does not save Appellants' claims, even if the judicial enforcement of contracts were not by operation of state law, because, as the Eighth Circuit held in *Bryant*, express-warranty claims implicating the safety or effectiveness of a PMA-approved medical device—such as the express-warranty claims asserted here—are, at the very least, *impliedly* preempted.[27] As the Eighth Circuit explained, "[t]o succeed" on such claims, plaintiffs "must persuade a jury that [the devices in question] were not safe and

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[26] Because implied warranties arise "by operation of law" (*Master Blaster, Inc. v. Dammann*, 781 N.W.2d 19, 35 (Minn. Ct. App. 2010 (citing Minn. Stat. §336.2-315), there can be no doubt that Appellants' implied warranty claims are expressly preempted. *See, e.g.*, *Riegel*, 552 U.S. at 327-29; *Caplinger*, 921 F.Supp.2d at 1222.

[27] Noting that *Cipollone v. Ligget Group, Inc.*, 505 U.S. 504 (1992), "construed a different, narrower express preemption provision" and that the lower courts are divided over the issue, the Eighth Circuit did not decide whether §360k(a) preempts express-warranty claims implicating the safety or effectiveness of PMA-approved devices, finding that it "need not decide that issue" given that such claims are in any event impliedly preempted. *Bryant*, 623 F.3d at 1207-08.

effective, a finding that would be contrary to the FDA's approval" of those devices through the PMA process. *Bryant*, 623 F.3d at 1207-08; *accord Ledet*, 2013 WL 6858858, at *6; *Gavin*, 2013 WL 3791612, at *15; *Caplinger*, 921 F.Supp.2d at 1222. For that reason, such "express warranty claim[s] interfere[] with the FDA's regulation of Class III medical devices and [are] therefore conflict preempted." *Bryant*, 623 F.3d at 1208.

Appellants' warranty claims are also impliedly preempted because they seek to enforce safety requirements different from those imposed by the FDA. Because such claims "'require[] a manufacturer's [device] to be safer, but hence less effective, than the model the FDA has approved,'" they necessarily "'disrupt[] the federal scheme'" and "interfere[] with the FDA's regulation of Class III medical devices." *Caplinger*, 921 F.Supp.2d at 1213, 1222 (quoting *Riegel*, 522 U.S. at 325). Allowing such claims to proceed would, contrary to congressional intent, give lay juries license to substitute their own "cost-benefit analysis" in place of "that applied by the experts at the FDA"—a task juries are ill-suited to perform because "[a] jury … sees only the cost of a more dangerous design, and is not concerned with its benefits" because

"the patients who reaped those benefits are not represented in court." *Riegel*, 552 U.S. at 325. Thus, warranty claims implicating the safety or effectiveness of a PMA-approved medical device—such as those asserted here—are preempted.

4. Appellants' negligence-*per-se* claims are impliedly preempted.

A negligence-*per-se* claim, by definition, depends on the alleged violation of a statutory provision, and therefore would not exist in the absence of that statute. Appellants' negligence-*per-se* claims are based on purported violations of the FDCA (Compl.¶198) and would not exist absent the FDCA. Thus, they "are simply an attempt by private parties to enforce the MDA." *Bryant*, 623 F.3d at 1205. "As a matter of law," therefore, Appellants' "negligence *per se* claims are preempted under 21 U.S.C. §337(a)." *In re Medtronic Sprint Fidelis Lead Prods. Liab. State Ct. Litig.*, 2009 WL 3417867, at *20 (Minn. Dist. Ct. 2009) (Reilly, J.); *accord, e.g.*, *In re Darvocet Prods. Liab. Litig.*, 756 F.3d 917, 936 (6th Cir. 2014); *In re Orthopedic Bone Screw Prods. Liab. Litig.*, 193 F.3d 781, 791 (3d Cir. 1999); *McClelland v. Medtronic, Inc.*, 944 F.Supp.2d 1193, 1200 (M.D. Fla. 2013).

II. APPELLANTS' FRAUD CLAIMS ARE NOT PLEADED WITH PARTICULARITY.

To date, the district court has considered the sufficiency of the fraud allegations in ten companioned cases. It has denied Medtronic's motions to dismiss in four of those cases, and granted it in the six cases currently before this Court. This closely split result reflects the care with which the district court has evaluated the specific allegations in each case. Because the district court was correct to conclude that Appellants failed to allege with particularity any purported misrepresentations that their surgeons relied on when deciding to use the Infuse device in their surgeries, and thus failed to satisfy Rule 9.02, the dismissal of Appellants' fraud claims should be affirmed.[28]

A. The District Court Employed The Correct Standard.

Appellants assert (Br.36-37) that the district court relied on this

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[28] In a telling approach, Appellants devote the majority of their argument *not* to explaining why *their* amended complaints satisfy Rule 9.02, but to summarizing out-of-state decisions where courts have accepted volume in place of particularity. *See* Br.43-48. Appellants also ignore *Martin* and *Beavers-Gabriel*, which dismissed as inadequately pleaded complaints (drafted by Appellants' counsel) nearly identical to Appellants' complaints. *See Martin*, 2014 WL 3635292, at *10; *Beavers-Gabriel,* 2014 WL 1396582, at *12-13. Those decisions, and those below, are in line with the weight of persuasive authority. *See, e.g.*, *Brady*, 2014 WL 1377830, at *8; *Hawkins*, 2014 WL 346622, at *13; *Kashani-Matts*, 2013 WL 6147032, at *5.

Court's decision in *Baker v. Best Buy Stores, LP*, 812 N.W.2d 177 (Minn. Ct. App. 2012), which they contend employed a particularity standard that is "stricter" than that required by Rule 9.02. The district court, however, relied not on *Baker*, but on the "arguably more permissive pleading standard of *Martens*." Add.69. Regardless, Appellants' assertion is a red herring. It does not matter (*cf.* Br.37) whether Rule 9.02 requires Appellants to plead the "who, what, when, where, and how" (*Baker*, 812 N.W.2d at 184) or the "ultimate facts" of the alleged fraud (*Hardin Cnty. Sav. Bank v. Hous. & Redev. Auth.*, 821 N.W.2d 184, 191 (Minn. 2012)). Appellants do not plead sufficient facts under any formulation.

B. Appellants Have Failed To Plead The Facts Underlying Each Element Of Fraud.

Accepting for purposes of argument Appellants' preferred formulation, Appellants must plead the "ultimate facts—or facts underlying each element" of their fraud claim. *Hardin*, 821 N.W.2d at 194. Thus, Appellants must, among other things, plead "with specificity" *facts* that, if true, would establish that Medtronic made a (1) "false" (2) "representation" of (3) "a past or present fact," which was (4) "reli[ed up]on." *Martens*, 616 N.W.2d at 747. Appellants have failed to

do so.

1. Appellants have not identified a false representation relied upon by their surgeons.

Appellants "allege[] that [Medtronic's] fraud occurred through [their] treating physician[s], who [were] on the receiving end of the alleged misrepresentations made by" Medtronic. Add.68; *accord* FAC¶200; Br.38. The district court was therefore correct that each Appellant "must plead facts to show that his or her physician was affirmatively misled" by Medtronic "in assessing the potential risk" from off-label use of the Infuse device and "relied on [the misrepresentation] in deciding to go ahead with the surgical procedure at issue." Add.109-110. The district court was also correct to conclude that Appellants have "identified no statements," in either their original complaints or their amended complaints, "that were allegedly false or misleading and that were relied upon by … their physicians." Add.110.

Insofar as Appellants' fraud claims rely on alleged misrepresentations in the medical literature, each Appellant's allegations are insufficient because they fail to "identify a specific article or articles containing alleged misrepresentations that [Appellant's surgeons] read and relied on in deciding to perform an off-

label procedure in [Appellant's] case." Add.87. Five of the Appellants' amended complaints allege only that their surgeons "relied on the available medical literature." FAC¶240(a); *see also* Br.14 n.19. But, as Appellants' complaints—which cite more than a dozen studies—attest, the medical literature regarding Infuse is vast. Therefore, as the district court held, "[g]eneric allegations that a physician read 'available medical literature' do not give [Medtronic] an opportunity to specifically understand and quickly defend against fraud claims based upon such literature." Add.70. Even if Appellants were not required to identify a particular misrepresentation upon their surgeons relied, surely they "must at least identify a specific article or articles containing alleged misrepresentations that [their surgeons] read and relied on." Add.70; *cf.* *Baker*, 812 N.W.2d at 183 (plaintiff must "reference … a specific" document).[29] Thus, even if one were to assume that Appellants had identified misrepresentations in the medical literature attributable to Medtronic, their fraud claims would still have to be dismissed because

[29] Appellant Manuel alleges that his surgeon "specifically recalled reading literature by Dr. Scott Boden and relying upon it." *Manuel* FAC¶239(a). But that hardly narrows the field, because Manuel admits that "Boden has written extensively on the use of Infuse® Bone Graft in off-label procedures." *Id.* ¶142.

"[m]issing from the Complaint[s] … is the connection between [Medtronic's] alleged misdeeds and … Plaintiff's physicians." *Beavers-Gabriel*, 2014 WL 1396582, at *12 (dismissing nearly identical Infuse-related fraud claim drafted by Appellants' counsel); *Martin*, 2014 WL 3635292, at *10 (same).

Appellants' claims would fail even if Appellants had identified specific articles on which their surgeons relied, because Appellants do not allege with particularity *any* false statements in *any* articles. Although the amended complaints identify various articles, they identify few specific statements within those articles, and do not adequately allege that any of those statements were "a false representation regarding a past or present fact." *Martens*, 616 N.W.2d at 747.[30]

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[30] For example, although the *Angeles* complaint alleges that one article "'conclude[d]'" that "'[n]o unanticipated device-related adverse events'" occurred when the Infuse device was used in a certain type of off-label procedure (FAC¶114(a) (quoting Haid, et al., *Posterior Lumbar Interbody Fusion Using Recombinant Human Bone Morphogenetic Protein Type 2 With Cylindrical Interbody Cages*, 4 Spine J. 527 (2004)), it does not allege that this statement was false when made. Indeed, it makes clear that the statement was carefully explained in the article, which informed readers that "reports of posterior bone formation are not considered *unanticipated* adverse device events since this was a possible adverse event listed in the risk analysis and informed consent

To the extent certain Appellants' claims rest on alleged misrepresentations purportedly made at medical conferences, the district court correctly found the allegations insufficient because Appellants—in addition to not identifying any specific statements made at any such conference—"have not named any of the alleged speakers in question, and … have not identified the date, or even the year of the conference[s]" at which the alleged misrepresentations were purportedly made. Add.9. Appellants do not dispute these findings, or explain how any complaint predicated on unidentified statements by unidentified persons at unidentified conferences has pleaded the "facts underlying each element" of a fraud claim. *Hardin*, 821 N.W.2d at 194.[31] Rule 9.02 is not satisfied where "[i]t is 'impossible to tell from the Complaint who made certain statements [and] what precisely was said.'" *Adams v. Rosensteel*, 2013 WL 6223562, at *4 (Minn. Ct. App.

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form." *Id.* (emphasis added). The complaint also ignores the article's cautionary conclusion that "[b]ecause of its small size, this study should be considered a pilot study" and that "larger PLIF studies with rhBMP-2 are needed." Haid, *supra*, 4 Spine J. at 536. R.Add.35.

[31] The Davenports are the only Appellants to have even vaguely identified a statement made at a conference, but "[t]he sole detail" recounted in their complaint—a slide supposedly showing a successful fusion in "a sheep's spine" using the Infuse device (*Davenport* FAC¶238(c))—"is not alleged to be untrue or misleading." Add.24-25.

2013).

Certain Appellants allege that Medtronic sales representatives either were "present in the operating room during [their] surgery" (*Marse* FAC¶238) or "instructed" their surgeons on off-label use of the Infuse device (*Davenport* FAC¶238). The district court correctly concluded that these allegations are insufficient to support Appellants' fraud claims because Appellants do "not identify any particular statement by" a sales representative (Add.39), and fail to allege that their respective surgeons "relied on anything said by a Medtronic representative in deciding to use the Infuse device in an off-label procedure" (Add.70).

2. Appellants must plead misrepresentations relied upon by their surgeons.

Although Appellants attempt to conflate off-label promotion and fraud (*see, e.g.*, Am.Compl.¶8 (quoted at Br.40)), "it is well-established that 'off-label marketing … is itself not inherently fraudulent.'" *Cent. Reg'l Emps. Benefit Fund v. Cephalon, Inc.*, 2009 WL 3245485, at *4 (D.N.J. 2009) (citing cases). Thus, Appellants must do more than allege Medtronic promoted off-label use; they must allege specific misrepresentations that were relied upon by their surgeons.

But rather than allege with particularity specific misrepresentations on which their surgeons relied, Appellants point to (unidentified) misrepresentations purportedly made to "the spine surgery community" at large. Br.3. Fraud, however, requires more than a misrepresentation; it requires a "'recipient'" who then "'rel[ies] on the misrepresentation.'" *Vogt v. Carriage Hills Golf Club*, 418 N.W.2d 536, 538 (Minn. Ct. App. 1988). Therefore, Appellants "must do more than simply allege that [Medtronic] engaged in a marketing program containing misrepresentations, of which … [Appellants'] surgeon[s] may or may not have been aware." *Rohlik v. I-Flow Corp.*, 2011 WL 2669302, at *3 (E.D.N.C. 2011). Rather, Appellants must "point to … affirmative representations made by [Medtronic] that were relied upon *by [their] physician[s]* when" deciding to use Infuse in their procedures. *Flynn*, 627 N.W.2d at 349-50 (emphasis added). Accordingly, it is not enough for Appellants to allege misrepresentations made to "the spine surgery community"; they must plead reliance by their surgeons in particular.[32]

[32] Although the "fraud-on-the-market" doctrine "presume[s] that investors who trade[] securities in [an efficient] market relied on public, material misrepresentations regarding those securities" (*Amgen Inc. v. Conn. Ret. Plans & Trust Funds*, 133 S.Ct. 1184, 1192 (2013)), the doctrine "is to be found nowhere in the … common law of fraud" (*id.* at

This they have not done.

Appellants' amended complaints "span over three-hundred paragraphs." Br. 38. But "prolixity" is no substitute for "particularity." *Ellis v. City of Minneapolis*, 2014 WL 3928525, at *2 (D. Minn. 2014). Nowhere in their complaints do Appellants plead "with specificity" (*Martens*, 616 N.W.2d at 747) the "ultimate facts" of Medtronic's alleged fraud (*Hardin*, 821 N.W.2d at 194).[33]

III. CERTAIN CLAIMS FAIL ON INDEPENDENT GROUNDS.

A. Appellants' Statutory Claims Fail.

Appellants' statutory claims—which sound in fraud, and must

1204 (Scalia, J., dissenting)), and has been universally rejected in the products-liability context, including specifically in the context of alleged off-label promotion of medical devices (*see, e.g.*, *In re Sofamor Danek Grp., Inc.*, 123 F.3d 394, 403-04 (6th Cir. 1997); *Bruzer v. Danek Med., Inc.*, 1998 WL 1048225, at *7 (D. Minn. 1998) (applying Minnesota law)).

[33] Starovasnik's complaint shares the defects common to the other Appellants' complaints and fails to satisfy Rule 9.02 for additional reasons. First, its "contradictory" (Add.53) allegations—that Starovasnik's surgeon was both a knowing participant in and an unwitting victim of Medtronic's alleged fraud—"impair [Medtronic's] ability to present a defense." *D & G Flooring, LLC v. Home Depot U.S.A., Inc.*, 346 F.Supp.2d 818, 822 (D. Md. 2004). Second, it "does not allege … any particular representations to [Starovasnik]" by his surgeon, "or that [Starovasnik] relied on … [such] representations in consenting to the surgery." Add.54. Third, it does not adequately allege that the surgeon was an agent of Medtronic acting within the scope of his agency when he made any representations to Starovasnik.

therefore satisfy Rule 9.02 (*Baker*, 812 N.W.2d at 183)—fail for the same reasons as Appellants' common-law fraud claims. *See supra* pp.57-65.

Appellants' claims under Minnesota statute also fail because the pursuit of monetary damages for alleged personal injuries is not a "matter[] of public interest." *Ly v. Nystrom*, 615 N.W.2d 302, 314 (Minn. 2000). Minnesota's Private Attorney General Statute (Minn. Stat. §8.31, subd. 3a) requires Appellants to demonstrate that their statutory claims "benefit[] the public." *Nystrom*, 615 N.W.2d at 314. "Here, [A]ppellants' complaint[s are] devoid of any allegations that [they were] brought for the 'public benefit' or how their action[s] benefit[] the public," and therefore must be dismissed. *Baker*, 812 N.W.2d at 183.

Where, as here, plaintiffs seek damages for "'personal injury, … alleg[ing] negligence and products liability,'" any statutory claims asserted are "meant to redress only the plaintiff's personal injuries," and therefore do "'not benefit the public.'" *Behrens v. United Vaccines, Inc.*, 228 F.Supp.2d 965, 971 (D. Minn. 2002). Thus, Appellants "'may not craft their products liability suit to bring it within the ambit of the Private AG Act.'" *Wehner v. Linvatech Corp.*, 2008 WL 495525, at *3 (D.

Minn. 2008).

Appellants' home-state statutory claims also fail. The statutes on which Davenport, Manuel Mead, and Starovasnik rely are limited to claims arising from goods purchased by a "consumer" for "personal, family, or household use." Ala. Code §8-19-3(2); 815 Ill. Comp. Stat. 505/1(e); Mo. Rev. Stat. §407.025(1); Or. Rev. Stat. §646.605(6)(a). Infuse, however, is not a consumer good for personal or household use. It is "restrict[ed] … to sale by or on the order of a physician" and "should only be used by surgeons who are experienced in spinal procedures." R.Add.16, 20; *see also, e.g.*, *In re Minnesota Breast Implant Litig.*, 36 F.Supp.2d 863, 876 (D. Minn. 1998). The statute on which Marse relies does *not* "apply to a cause of action for bodily injury." Tex. Bus. & Com. Code §17.49(e).

B. Appellants' Warranty Claims Fail.

Appellants' warranty claims fail, because Medtronic disclaimed all warranties, as permitted by law. *See* Minn. Stat. §336.2-316. Infuse's FDA-approved label states that "[n]o warranties, express or implied, are made" and that "[i]mplied warranties of merchantability and fitness for a particular purpose or use are specifically excluded." R.Add.18. This

unambiguous disclaimer defeats any warranty claim. *See Scanlon*, 2014 WL 3737501, at *7 (dismissing warranty claim arising from off-label use of Infuse given "conspicuous disclaimer of all warranties").

And, because Appellants do not identify "[a]ny affirmation of fact or promise made by" Medtronic or any "description of the" Infuse device that were allegedly "part of the basis of the bargain" (Minn. Stat. §336.2-313(1)), their express-warranty claims are inadequately pleaded.

CONCLUSION

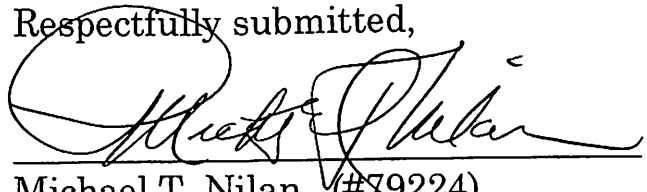
The judgments below should be affirmed.

RULE 132.01 CERTIFICATION

This brief was prepared using Microsoft Word 2007. The brief complies with the typeface requirements and contains 13,994 words.

DATED: September 8, 2014

Respectfully submitted,



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RESPONDENTS' ADDENDUM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JUL - 2 2002

Richard W. Treharne, Ph.D.
Senior Vice President, Regulatory Affairs
Medtronic Sofamor Danek
1800 Pyramid Place
Memphis, Tennessee 38132

Re: P000058
InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device
Filed: January 12, 2001
Amended: January 12, March 19, May 9, July 31, August 24, September 25, October 9, November 21, and December 6, 7 and 26, 2001, January 22, February 8, March 19, April 2, 3, 12 (2), 15, 16, 17, 22, 26 and 30, May 9, 10, 14 and 28 and June 12 and 28, 2002
Procode: NEK

Dear Dr. Treharne:

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 InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device. This device is indicated for spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at one level from L4-S1. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history, function deficit and/or neurological deficit and radiographic studies. These DDD patients may also have up to Grade I spondylolisthesis at the involved level. InFUSE™ Bone Graft/LT-CAGE™ devices are to be implanted via an anterior open or an anterior laparoscopic approach. Patients receiving the InFUSE™ Bone Graft/ LT-CAGE™ Lumbar Tapered Fusion Device should have had at least six months of nonoperative treatment prior to treatment with the InFUSE™ Bone Graft/LT-CAGE™ device. We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions described below and in the "Conditions of Approval" (enclosed).

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that, to ensure the safe and effective use of the device, the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

In addition to the post-approval requirements outlined in the enclosure, you have agreed to provide the following data in a post-approval report:

1. In order to assess the long-term performance of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device, please conduct a post-approval study to obtain a total of 6 years of postoperative data from a statistically-justified number of patients implanted with this device. The patients may be selected from either the IDE population, a population of post-approval implant patients or a combination of both.

   a. As part of the description of the post-approval study, you should provide a justification which includes:

      (1) the number of patients selected from each population (IDE vs. post-approval population);

      (2) the method(s) used to select the patients and sites; and

      (3) a description of the sample size calculations, including adjustments for lost-to-follow-up.

   b. The data from the post-approval study should be submitted to the FDA as part of your annual report and will include the following data collected biennially for each patient:

      (1) a description of any surgical interventions which include reoperations, removals, revisions, and supplemental fixations;

      (2) a radiographic assessment of fusion using the same criteria employed in the original IDE study;

      (3) an assessment of pain and function using the same criteria employed in the original IDE study.

2. Because of the unknown long-term device performance, particularly the resulting bony fusion characteristics, the post-approval study should also contain retrieval analyses of any InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device that is implanted and subsequently removed. This section of the post-approval study is not limited to the patient population described in item 1 above. Histological information (*e.g.*, bony ingrowth quality, bone quantity, response to potential wear debris, etc.) and metallurgical information (*e.g.*, metal wear, deformation, cracking, corrosion, etc.) should be collected and reported in the annual reports. This section of the post-approval study should continue for the duration of the study described in item 1 above.

3. Perform post-approval studies which assess the effects of rhBMP-2 on tumor promotion. These studies will include *in vitro* studies with primary tumor cell isolates.

4. Perform post-approval studies to investigate the potential for an immune response to rhBMP-2 to interfere in embryonic development in rabbits. Observations from this investigation may indicate a necessity to create a pregnancy monitoring database and/or modify your labeling.

5. Develop and validate a new antibody ELISA for antibodies to rhBMP-2 that has the potential to detect all antibody isotypes.

6. Develop and validate a neutralization assay for antibodies to rhBMP-2.

Complete final reports addressing the requests identified in items 3-6 above should be submitted as the reports become available. If these reports have not been submitted by the time of submission of the first PMA annual report, you should include an approximate timeline for submission in the annual reports, as well as updates on the studies' progress.

7. Provide the results of three additional assays, *i.e.*, silver stained SDS-PAGE, Edmans test and glycoform analysis, on the release specifications for the drug substance. These should be submitted as PMA reports.

Expiration dating for this device has been established and approved at three years for the Small and Medium InFUSE™ Bone Graft components, two years for the Large and Large II InFUSE™ Bone Graft components and five years for the LT-CAGE™ Lumbar Tapered Fusion Device component.

CDRH does not evaluate information related to contract liability warranties, however you should be aware that any such warranty statements must be truthful, accurate, and not misleading, and must be consistent with applicable Federal and State laws.

CDRH will notify the public of its decision to approve your PMA by making available a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at http://www.fda.gov/cdrh/pmapage.html. Written requests for this information can also be made to the Dockets Management Branch, (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

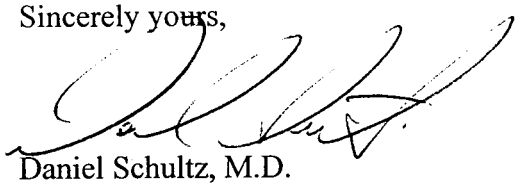
You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. The labeling will not routinely be reviewed by FDA staff when PMA applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Mr. Aric D. Kaiser at (301) 594-2036.

Sincerely yours,



Daniel Schultz, M.D.
Deputy Director for Clinical
and Review Policy
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Last Modified: 1-31-02

CONDITIONS OF APPROVAL

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e) or (f). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations that require a PMA supplement cannot be briefly summarized; therefore, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report (see below). FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

Alternate submissions permitted under 21 CFR 814.39(f) for manufacturing process changes include the use of a 30-day Notice. The manufacturer may distribute the device 30 days after the date on which the FDA receives the 30-day Notice, unless the FDA notifies the applicant within 30 days from receipt of the notice that the notice is not adequate.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

1. Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

2. Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

   a. unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

   b. reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

1. A mix-up of the device or its labeling with another article.

2. Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and:

   a. has not been addressed by the device's labeling; or

   b. has been addressed by the device's labeling but is occurring with unexpected severity or frequency.

3. Any significant chemical, physical or other change or deterioration in the device, or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION.
The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984. This regulation was replaced by the reporting requirements of the Safe Medical Devices Act of 1990 which became effective July 31, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to the FDA whenever they receive or otherwise become aware of information, from any source, that reasonably suggests that a device marketed by the manufacturer or importer:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for a PMA, the manufacturer shall submit the appropriate reports required by the MDR Regulation within the time frames as identified in 21 CFR 803.10(c) using FDA Form 3500A, i.e., 30 days after becoming aware of a reportable death, serious injury, or malfunction as described in 21 CFR 803.50 and 21 CFR 803.52 and 5 days after becoming aware that a reportable MDR event requires remedial action to prevent an unreasonable risk of substantial harm to the public health. The manufacturer is responsible for submitting a baseline report on FDA Form 3417 for a device when the device model is first reported under 21 CFR 803.50. This baseline report is to include the PMA reference number. Any written report and its envelope is to be specifically identified, e.g., "Manufacturer Report," "5-Day Report," "Baseline Report," etc.

Any written report is to be submitted to:

Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting
PO Box 3002
Rockville, Maryland 20847-3002

Copies of the MDR Regulation (FOD # 336&1336)and FDA publications entitled "An Overview of the Medical Device Reporting Regulation" (FOD # 509) and "Medical Device Reporting for Manufacturers" (FOD #987) are available on the CDRH WWW Home Page. They are also available through CDRH's Fact-On-Demand (F-O-D) at 800-899-0381. Written requests for information can be made by sending a facsimile to CDRH's Division of Small Manufacturers International and Consumer Assistance (DSMICA) at 301-443-8818.

Premarket Approval (PMA)

Note: this medical device has supplements. The device description may have changed.
Be sure to look at the supplements to get an up-to-date view of this device.

Trade Name	INFUSE BONE GRAFT/LT-CAGE LUMBAR TAPERED FUSION DEVICE
Classification Name	Filler, Recombinant Human Bone Morphogenetic Protein, Collagen Scaffold With Metal Prosthesis, Osteoinduction[22]
Applicant	MEDTRONIC SOFAMOR DANEK USA, INC.
PMA Number	P000058
Date Received	12/22/2000
Decision Date	07/02/2002
Product Code	NEK [Registered Establishments With NEK[23]]
Docket Number	02M-0310
Notice Date	07/11/2002
Advisory Committee	Orthopedic
Expedited Review Granted?	Yes
Combination Product	Yes[24]
Information About:	Labeling, Approval Order, Summary Of Safety And Effectiveness[25]
Recalls	CDRH Recalls[26]

Approval Order Statement

Approval for the infuse bone graft/lt-cage lumbar tapered fusion device. This device is indicated for spinal fusion procedures in skeletally mature patients with degenerative disc disease (ddd) at one level from l4-s1. Ddd is defined as discogenic back pain with degeneration of the disc confirmed by patient history, function deficit and/or neurological deficit and radiographic studies. These ddd patients may also have up to grade i spondylolisthesis at the involved level. Infuse bone graft/lt-cage devices are to be implanted via an anterior open or an anterior laparoscopic approach. Patients receiving the infuse bone graft/lt-cage lumbar tapered fusion device should have had at least six months of nonoperative treatment prior to treatment with the infuse bone graft/lt-cage device.

Approval Order Approval Order[27]

Supplements:

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S010[37] S014[38] S015[39] S016[40] S017[41] S019[42] S020[43] S021[44] S022[45]
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InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device
Important Medical Information

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician with appropriate training.

DESCRIPTION:

The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device consists of two components containing three parts– a tapered metallic spinal fusion cage, a recombinant human bone morphogenetic protein and a carrier/scaffold for the bone morphogenetic protein and resulting bone. The InFUSE™ Bone Graft component is inserted into the LT-CAGE™ Lumbar Tapered Fusion Device component to form the complete InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device. **These components must be used as a system. The InFUSE™ Bone Graft component must not be used without the LT-CAGE™ Lumbar Tapered Fusion Device component.**

LT-CAGE™ Lumbar Tapered Fusion Device component

The LT-CAGE™ device consists of a hollow, perforated, machined cylinder with opposing flat sides. The cage has a tapered design with an angle of 8.8° and is available in diameters ranging from 14mm to 18mm at the narrow end of the taper, 17mm to 22 mm at the wide end of the taper and in lengths ranging from 20mm to 26mm. There are two holes on each of the two flat sides. On each of the two rounded aspects, there is a single rounded slot. The implants have a helical screw thread on the outer surface. One end of the device is closed. The other end is open to be filled with the InFUSE™ Bone Graft component.

The LT-CAGE™ implants are made from implant grade titanium alloy (Ti-6Al-4V) described by such standards as ASTM F136 or its ISO equivalent.

The LT-CAGE™ Lumbar Tapered Fusion Device component is sold separately from the InFUSE™ Bone Graft component, however, these two components must be used together. The package labeling for the LT-CAGE™ Lumbar Tapered Fusion Device contains complete product information for this component.

InFUSE™ Bone Graft component

InFUSE™ Bone Graft consists of recombinant human Bone Morphogenetic Protein-2 (rhBMP-2, known as dibotermin alfa) placed on an absorbable collagen sponge (ACS). The InFUSE™ Bone Graft component induces new bone tissue at the site of implantation. Based on data from non-clinical studies, the bone

formation process develops from the outside of the implant towards the center until the entire InFUSE™ Bone Graft component is replaced by trabecular bone.

rhBMP-2 is the active agent in the InFUSE™ Bone Graft component. rhBMP-2 is a disulfide-linked dimeric protein molecule with two major subunit species of 114 and 131 amino acids. Each subunit is glycosylated at one site with high-mannose-type glycans. rhBMP-2 is produced by a genetically engineered Chinese hamster ovary cell line.

rhBMP-2 and excipients are lyophilized. Upon reconstitution, each milliliter of rhBMP-2 solution contains: 1.5 mg of rhBMP-2; 5.0 mg sucrose, NF; 25 mg glycine, USP; 3.7 mg L-glutamic acid, FCC; 0.1 mg sodium chloride, USP; 0.1 mg polysorbate 80, NF; and 1.0 mL of sterile water. The reconstituted rhBMP-2 solution has a pH of 4.5, and is clear, colorless and essentially free from plainly visible particulate matter.

The ACS is a soft, white, pliable, absorbent implantable matrix for rhBMP-2. ACS is made from bovine Type I collagen obtained from the deep flexor (Achilles) tendon. The ACS acts as a carrier for the rhBMP-2 and acts as a scaffold for new bone formation.

Three sizes of the InFUSE™ Bone Graft component are available based on the internal volume of the LT-CAGE™ Lumbar Tapered Fusion Device component that is selected. The table below lists the appropriate InFUSE™ Bone Graft kit for the corresponding LT-CAGE™ Lumbar Tapered Fusion Device component size:

InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device Combinations				
LT-CAGE™ Lumbar Tapered Fusion Device		**Appropriate InFUSE™ Bone Graft Kit**		
Part #	Size (lead diameter, mm x length, mm)	Part #	Kit name (size in cc)	Reconstituted rhBMP-2/ACS graft volume
8941420	14x20	7510200	Small (2.8)	2.8ml
8941423	14x23	7510200	Small (2.8)	2.8ml
8941620	16x20	7510200	Small (2.8)	2.8ml
8941623	16x23	7510400	Medium (5.6)	5.6ml
8941626	16x26	7510400	Medium (5.6)	5.6ml
8941823	18x23	7510400	Medium (5.6)	5.6ml
8941826	18x26	7510600	Large Pre-Cut (8.0)	8.0ml
8941826	18x26	7510800	Large II (8.0)	8.0ml

Each kit contains all the components necessary to prepare the InFUSE™ Bone Graft component: the rhBMP-2 which must be reconstituted, sterile water, absorbable collagen sponges, syringes with needles, this package insert and

instructions for preparation. The number of each item may vary depending on the size of the kit.

The rhBMP-2 is provided as a lyophilized powder in vials delivering either 4.2 mg or 12 mg of protein. After appropriate reconstitution, both configurations result in the same formulation and concentration (1.5 mg/mL) of rhBMP-2. The solution is then applied to the provided absorbable collagen sponge(s). The InFUSE™ Bone Graft component is prepared at the time of surgery and allowed a prescribed amount of time (no less than 15 minutes) before placement inside of the LT-CAGE™ Lumbar Tapered Fusion Device components. The Instructions for Preparation contain complete details on preparation of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device.

No warranties, express or implied, are made. Implied warranties of merchantability and fitness for a particular purpose or use are specifically excluded.

INDICATIONS:

The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device is indicated for spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at one level from L_4-S_1. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history and radiographic studies. These DDD patients may also have up to Grade I spondylolisthesis at the involved level. Patients receiving the InFUSE™ Bone Graft/ LT-CAGE™ Lumbar Tapered Fusion Device should have had at least six months of nonoperative treatment prior to treatment with the InFUSE™ Bone Graft/LT-CAGE™ device. The InFUSE™ Bone Graft/ LT-CAGE™ Lumbar Tapered Fusion Device is to be implanted via an anterior open or an anterior laparoscopic approach.

CONTRAINDICATIONS

- The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device is contraindicated for patients with a known hypersensitivity to recombinant human Bone Morphogenetic Protein-2, bovine Type I collagen or to other components of the formulation.

- The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device should not be used in the vicinity of a resected or extant tumor.

- InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device should not be used in patients who are skeletally immature (<18 years of age or no radiographic evidence of epiphyseal closure).

- The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device should not be used in pregnant women. The potential effects of rhBMP-2 on the human fetus have not been evaluated.

- The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device should not be implanted in patients with an active infection at the operative site or with an allergy to titanium or titanium alloy.

WARNINGS:

- Women of childbearing potential should be advised that antibody formation to rhBMP-2 or its influence on fetal development have not been assessed. In the clinical trial supporting the safety and effectiveness of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device, 2/277 (0.7%) patients treated with InFUSE™ Bone Graft component and 1/127 (0.8%) patients treated with autograft bone developed antibodies to rhBMP-2. The effect of maternal antibodies to rhBMP-2, as might be present for several months following device implantation, on the unborn fetus is unknown. Additionally, it is unknown whether fetal expression of BMP-2 could re-expose mothers who were previously antibody positive, thereby eliciting a more powerful immune response to BMP-2 with adverse consequences for the fetus. Studies in genetically altered mice indicate that BMP-2 is critical to fetal development and that lack of BMP-2 activity, as might be induced by antibody formation, may cause neonatal death or birth defects.

- The safety and effectiveness of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device in nursing mothers has not been established. It is not known if BMP-2 is excreted in human milk.

- Women of childbearing potential should be advised not to become pregnant for one year following treatment with the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device.

- The safety and effectiveness of the InFUSE Bone Graft component with other spinal implants, implanted at locations other than the lower lumbar spine, or used in surgical techniques other than anterior open or anterior laparoscopic approaches have not been established. When degenerative disc disease was treated by a posterior lumber interbody fusion procedure with cylindrical threaded cages, posterior bone formation was observed in some instances.

- The implantation of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device using an anterior laparoscopic surgical approach is associated with a higher incidence of retrograde ejaculation when compared to implantation using the an anterior open surgical approach.

PRECAUTIONS:

General

- The safety and effectiveness of repeat applications of the InFUSE™ Bone Graft component has not been established.

- The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device should only be used by surgeons who are experienced in spinal fusion procedures and have undergone adequate training with this device, for anterior laparoscopic and/or anterior open procedures.

- Two LT-CAGE™ Lumbar Tapered Fusion Device components should be implanted side by side at the surgical level whenever possible.

- The LT-CAGE™ Lumbar Tapered Fusion Device components and instruments must be sterilized prior to use according to the sterilization instructions provided in the package insert for that component, unless supplied sterile and clearly labeled as such.

- The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device is intended for single use only. Discard unused product and use a new device for subsequent applications.

- Prior to use, inspect the packaging, vials and stoppers for visible damage. If damage is visible, do not use the product. Retain the packaging and vials and contact a Medtronic Sofamor Danek representative.

- Do not use after the printed expiration date on the label.

Hepatic and Renal Impairment

- The safety and effectiveness of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device in patients with hepatic or renal impairment has not been established. Pharmacokinetic studies of rhBMP-2 indicate that the renal and hepatic systems are involved with its clearance.

Geriatrics

- Clinical studies of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device did not include sufficient numbers of patients 65 years and older to determine whether they respond differently from younger subjects.

Bone formation

- The safety and effectiveness of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device has not been demonstrated in patients with metabolic bone diseases.

- While not specifically observed in the clinical study, the potential for ectopic, heterotopic or undesirable exuberant bone formation exists.

Antibody Formation/Allergic Reactions

- The safety and effectiveness of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device has not been demonstrated in patients with autoimmune disease.

- The safety and effectiveness of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device has not been demonstrated in patients with immunosuppressive disease or suppressed immune systems resulting from radiation therapy, chemotherapy, steroid therapy or other treatments.

Immunogenicity

- As with all therapeutic proteins, there is a potential for immune responses to be generated to the InFUSE™ Bone Graft component. The immune response to the InFUSE™ Bone Graft components was evaluated in 349 investigational patients and 183 control patients receiving lumbar interbody fusions.

    - *Anti-rhBMP-2 antibodies:* 2/349 (0.6%) patients receiving the InFUSE™ Bone Graft component developed antibodies vs. 1/183 (0.5%) in the control group.

    - *Anti-bovine Type I collagen antibodies:* 18.1% of patients receiving the InFUSE™ Bone Graft component developed antibodies to bovine Type I collagen vs. 14.2% of control patients. No patients in either group developed anti-human Type I collagen antibodies.

    - The presence of antibodies to rhBMP-2 was not associated with immune mediated adverse events such as allergic reactions. The neutralizing capacity of antibodies to rhBMP-2 is not known.

- The incidence of antibody detection is highly dependent on the sensitivity and specificity of the assay. Additionally, the incidence of antibody detection may be influenced by several factors including sample handling, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to the InFUSE™ Bone Graft component with the incidence of antibodies to other products may be misleading.

ADVERSE EVENTS:

The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device was implanted in 288 investigational patients and compared to 139 control patients who received an LT-CAGE™ Lumbar Tapered Fusion Device filled with iliac crest autograft. The investigational patients were implanted with the device via either an open anterior surgical approach or a laparoscopic anterior surgical approach. The control patients were implanted only via the open anterior surgical approach.

Adverse event rates presented are based on the number of patients having at least one occurrence for a particular adverse event divided by the total number of patients in that treatment group.

ADVERSE EVENTS

(INFUSE™ Bone Graft/LT-Cage™ Device data combined from all experience with the device)

	Surgery		Postoperative (1 day - <4 Weeks)		6 Weeks (≥4 Wks - <9 Weeks)		3 Months (≥9 Wks - <5 Months)		6 Months (≥5 Mos - <9 Months)		12 Months (≥9 Mos - <19 Months)		24 Months (≥19 Mos - <30 Months)		# of Patients Reporting & Total adverse events	
Complication	Inves.	Control	Inves.	Control	Inves.	Control	Inves.	Control	Inves.	Control	Inves.	Control	Inves.	Control	Investigational # (% of 288) total events	Control #(% of 139) total events
Anatomical/Technical Difficulty	10	3	0	0	0	0	0	0	0	0	0	0	0	0	10 (3.5) 10	3 (2.2) 3
Back and/or Leg Pain	0	0	1	4	11	5	10	5	14	4	20	7	6	8	65 (22.6) 72	30 (21.6) 33
Cancer	0	0	0	0	0	0	0	1	0	0	1	0	0	0	1 (0.3) 1	1 (0.7) 1
Cardio/Vascular	2	0	4	5	6	2	1	3	2	1	3	2	0	1	15 (5.2) 18	12 (8.6) 14
Death	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0 (0.0) 0	1 (0.7) 1
Dural Injury	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0 (0.0) 0	1 (0.7) 1
Gastrointestinal	1	0	38	22	2	0	5	1	7	1	9	3	4	5	53 (18.4) 67	27 (19.4) 32
Graft Site Related	0	0	0	0	0	8	0	0	0	0	0	0	0	0	0 (0.0) 0	8 (5.8) 8
Implant Displacement/ Loosening	0	0	1	1	3	0	1	0	0	0	0	0	0	0	5 (1.7) 5	1 (0.7) 1
Infection	0	0	19	9	8	4	4	1	5	1	3	0	0	2	35 (12.2) 39	16 (11.5) 17
Malpositioned Implant	5	0	0	0	0	0	0	0	0	0	0	0	0	0	5 (1.7) 5	0 (0.0) 0
Neurological	0	0	7	5	7	3	5	2	5	2	10	3	5	7	36 (12.5) 39	21 (15.1) 22
Non-Union *	0	0	0	0	0	0	1	0	1	3	2	0	1	1	5 (1.7) 5	4 (2.9) 4
Non-Union **	0	0	0	1	0	1	3	0	3	4	4	6	1	1	11 (3.8) 11	13 (9.4) 13
Other	6	6	17	11	7	2	3	4	8	4	14	8	9	8	50 (17.4) 64	37 (26.6) 43
Other Pain	0	0	1	1	2	0	4	2	5	1	7	6	6	3	21 (7.3) 25	12 (8.6) 13
Respiratory	0	0	3	2	1	0	0	0	1	0	0	1	0	1	5 (1.7) 5	4 (2.9) 4
Retrograde Ejaculation	0	0	4	1	5	0	1	0	0	0	2	0	0	0	11 (7.9)[1] 12	1 (1.4)[2] 1
Spinal Event	0	0	1	2	0	0	6	2	8	3	8	8	4	2	24 (8.3) 27	16 (11.5) 17
Subsidence	0	0	3	2	2	0	1	0	1	0	0	0	0	0	7 (2.4) 7	2 (1.4) 2
Trauma	0	0	4	4	5	3	11	6	14	5	27	9	11	7	60 (20.8) 72	29 (20.9) 34
Urogenital	1	0	20	5	2	0	2	2	6	1	2	1	4	2	33 (11.5) 37	10 (7.2) 11
Vascular Intra-Op	15	5	0	0	0	0	0	0	0	0	0	0	0	0	14 (4.9) 15	5 (3.6) 5
Vertebral Fracture	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1 (0.3) 1	0 (0.0) 0
Any Adverse Event															214 (74.3)	114 (82.0)

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* Non-union adverse events that have not resulted in a second surgery.

** Non-union adverse events that have resulted in a second surgery.

[1] Percent of 140 males.

[2] Percent of 70 males.

The reported rates of several adverse events were high, but similar, in both the investigational and control groups. These events included back and leg pain, neurological events, gastrointestinal events, spinal events, cardiovascular events and infection.

Some of the reported adverse events required surgical interventions subsequent to the initial surgery. The number of subjects requiring a second surgical intervention was 10.4% (30/288) in the investigational groups and 13.7% (19/139) in the control group. The majority of supplemental fixations were due to painful nonunion.

Urogenital events occurred with greater frequency in the investigational groups (11.5%) compared to the control group (7%). Retrograde ejaculation rates were greater in the investigational groups (11 subjects) compared to the control group (1 subject) with the majority of events occurring in the early postoperative period.

The incidence of adverse events that were considered device related, including implant displacement/loosening, implant malposition and subsidence were all greater in the investigational groups compared to the control group. The rates of these events were low, however, and may be partially attributed to a learning curve associated with the laparoscopic surgical approach. The rate of nonunion requiring secondary surgery in the investigational groups was comparable to that of the control group. One death was reported - a control group subject with cardiovascular disease.

Potential Adverse Events:

The following is a list of potential adverse events which may occur with spinal fusion surgery with the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device. Some of these adverse events may have been previously reported in the adverse events table.

- Bone fracture.
- Bowel or bladder problems.
- Cessation of any potential growth of the operated portion of the spine. Loss of spinal mobility or function.
- Change in mental status.
- Damage to blood vessels and cardiovascular system compromise.
- Damage to internal organs and connective tissue.
- Death.

- Development of respiratory problems.
- Disassembly, bending, breakage, loosening, and/or migration of components.
- Dural tears.
- Ectopic and/or exuberant bone formation.
- Fetal development complications.
- Foreign body (allergic) reaction.
- Gastrointestinal complications.
- Incisional complications.
- Infection.
- Insufflation complications.
- Neurological system compromise.
- Nonunion (or pseudarthrosis), delayed union, mal-union.
- Postoperative change in spinal curvature, loss of correction, height, and/or reduction.
- Retrograde ejaculation.
- Scar formation.
- Tissue or nerve damage.

Note: Additional surgery may be necessary to correct some of these potential adverse events.

CLINICAL RESULTS:

Clinical data to support the safety and effectiveness of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device were collected as part of a prospective, multi-center pivotal study that consisted of randomized and non-randomized arms. The randomized arm contained two groups, one investigational and one control. The control group was implanted with the LT-CAGE™ Lumbar Tapered Fusion Device filled with iliac crest autograft bone, while the investigational group was implanted with the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device. In both

cases, the surgical approach was an open anterior approach. The non-randomized arm contained only an investigational group, where subjects were implanted with the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device through a laparoscopic anterior approach. The control group from the randomized arm was used as the control for the non-randomized arm.

Neither the investigators nor the subjects were blinded to the treatment. Subject blinding was not possible due to the second surgical site resulting from the need to collect the iliac crest grafts. The potential for investigator bias in the clinical outcome parameters was reduced by having the subjects rate their outcome using objective self-assessments. The radiographic outcome parameters were performed by independent radiologists who were blinded to treatment. These were the only radiographic evaluations used for determining radiographic success.

The indication studied was degenerative disc disease (DDD) accompanied by back pain with or without leg pain at a single level between L_4 and S_1 confirmed by history and radiographic studies.

Clinical and radiographic effectiveness parameters

Patients were evaluated preoperatively (within 6 months of surgery), intraoperatively, and postoperatively at 6 weeks, 3, 6, 12 and 24 months and biennially thereafter until the last subject enrolled in the study had been seen for their 24 month evaluation. Complications and adverse events, device-related or not, were evaluated over the course of the clinical trial. At each evaluation timepoint, the primary and secondary clinical and radiographic outcome parameters were evaluated. Success was determined from data collected during the initial 24 months of follow-up. Antibodies to rhBMP-2 and bovine Type I collagen were assessed preoperatively and at 3 months post-operatively. Antibodies to human Type I collagen were assessed if the antibody response to bovine Type I collagen was positive.

Primary and secondary clinical and radiographic effectiveness outcome parameters were evaluated for all treated subjects at all follow-up evaluation timepoints identified above. The primary clinical parameters assessed were of pain, function and neurological status. The secondary clinical outcome parameters assessed were general health status, back and leg pain, donor site pain (control subjects only), patient satisfaction and patient global perceived effect of the treatment. The primary radiographic outcome parameter consisted of evaluations of fusion, while the secondary radiographic assessment was disc height.

Fusion was evaluated at 6, 12 and 24 months post-op using plain radiographs (AP, lateral and flexion/extension films) and high resolution thin-slice CT scans (1mm slices with 1mm index on axial sagittal and coronal reconstructions). Fusion was defined as the presence of bridging bone connecting the inferior and superior

vertebral bodies; a lack of motion on flexion/extension (≤ 3mm of translation and < 5° of angulation); and no evidence of radiolucencies over more that 50% of either implant. Fusion success was defined as the presence of all of these parameters plus the lack of a second surgical intervention resulting from a non-union. All assessments were made from the plain films except for the assessment of bridging bone, which was made using the CT scans only if bridging bone could not be visualized on the plain film.

Pain and function were measured using the Oswestry Low Back Pain Disability Questionnaire. Success was defined as a 15 point improvement in the Oswestry score from the pre-op baseline score.

Neurological status consisted of measurements of four parameters - motor, sensory, reflexes, and straight leg raise (SLR). Neurological status success was defined as maintenance or improvement of the pre-op baseline score for each parameter. Overall neurological status success required that each individual parameter be a success for that subject to be counted as a success.

Patient demographics and accountability

A total of 143 open approach investigational and 136 control patients were enrolled in the randomized arm of the study and received the device. A total of 134 subjects were enrolled in the non-randomized arm of the study and received the device. For the majority of the demographic parameters, there were no differences in pre-op demographics across the three populations.

Surgical results and hospitalization

Surgical and hospitalization information			
	Investigational Open Surgical Approach	Control Open Surgical Approach	Investigational Laparoscopic Surgical Approach
mean operative time (hrs)	1.6	2.0	1.9
mean EBL (ml)	109.8	153.1	146.1
hospitalization (days)	3.1	3.3	1.2

statistically different from control

Clinical and radiographic effectiveness evaluation

Individual subject success was defined as success in each of the primary clinical and radiographic outcome parameters. Success for these parameters included:

1. the presence of radiographic fusion;
2. an improvement of at least 15 points from the baseline Oswestry score;
3. maintenance or improvement in neurological status;
4. the presence of no serious adverse event classified as implant-associated or implant/surgical procedure-associated; and
5. no additional surgical procedure classified as "Failure."

Study success was expressed as the number of individual subjects categorized as a success divided by the total number of subjects evaluated. The table below describes the success rates for the individual primary outcome parameters and overall success. All success rates were based on the data from the 24 month follow-up evaluation and posterior probabilities of success were calculated using Bayesian statistical methods.

Posterior Probabilities of Success at 24 Months			
Primary outcome variable	**Investigational Open Surgical Approach**	**Control Open Surgical Approach**	**Investigational Laparoscopic Surgical Approach**
	Posterior Mean (95% HPD Credible Interval)	Posterior Mean (95% HPD Credible Interval)	Posterior Mean (95% HPD Credible Interval)
Fusion	92.8% (88.5%, 96.9%)	88.1% (82.6%, 99.3%)	93.0% (87.9%, 97.5%)
Oswestry	71.0% (63.4%, 78.7%)	70.9% (63.1%, 79.1%)	83.0% (75.6%, 90.5%)
Neurologic	81.0% (74.5%, 87.9%)	81.7% (74.9%, 88.7%)	89.0% (83.1%,94.8%)
Overall success	57.1% (49.2%, 65.7%)	56.7% (48.3%, 65.0%)	68.0% (59.3%, 76.5%)

The probability (also called the posterior probability) that the 24 month overall success rate for the investigational groups was equivalent to the 24 month success rate for the control group was 99.4% for the open surgical approach investigational group and almost 100% for the laparoscopic surgical approach investigational group.

For a future patient receiving the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device via the open anterior surgical approach, the chance (the predictive probability) of overall success at 24 months would be 57.1% for the open surgical approach. Given the results of the trial, there is a 95% probability that the chance of success ranges from 49.2% to 65.7%. For a future patient receiving the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device via the anterior laparoscopic surgical approach, the chance of overall success at 24 months would be 68.0%. Given the results of the trial, there is a 95% probability that the chance of success ranges from 59.3% to 76.5%. For a future patient receiving the control treatment, the chance of overall success at 24 months would be 56.7%. Given the results of the trial, there is a 95% probability that the chance of success ranges from 48.3% to 65.0%.

Safety and immune response evaluation

The assessment of safety consisted of an evaluation of the reported adverse events, as well as an evaluation of antibodies to rhBMP-2, bovine Type I collagen and human Type I collagen. The complete list of complications, adverse events and subsequent interventions is described in the Adverse Events section above. The presence of antibodies were assessed at the pre-op and 3 month post-op visits using ELISA. If there was a positive response to bovine Type I collagen, the serum was also tested for antibodies to human Type I collagen. The screening ELISA cutpoint for positive

antibody responses was set to 5 times the standard deviation of sera from normal human donors. Subjects were considered to have an elevated immune response if the preoperative test was negative (titer < 50) and postoperative test was positive (titer ≥ 50) or if the preoperative test was positive and the postoperative test was positive with a three-fold higher titer than the preoperative test.

There were 3 subjects who had positive antibody responses to rhBMP-2 – 1 subject in each of the study groups. The rates of positive antibody response to rhBMP-2 were 0.7% in the open surgical approach investigational group and 0.8% in the laparoscopic surgical approach investigational and open surgical approach control groups. While there is a theoretical possibility that antibodies to rhBMP-2 could neutralize endogenous BMP-2, thereby interfering with subsequent bone healing, this was not observed during the course of the study.

Sixty-six subjects were considered to have an authentic elevated antibody response to bovine Type I collagen - 18 open surgical approach investigational subjects, 32 laparoscopic surgical approach investigational subjects and 16 control subjects. No subjects had positive responses to human Type I collagen.

An evaluation was performed on the impact of a positive antibody response on overall success and fusion success. There was very little difference in overall and individual success when antibody status was taken into consideration.

During the course of the study, 6 pregnancies were reported – one in the control group and five in the investigational groups. Two of the four pregnancies that occurred in the laparoscopic approach group resulted in first trimester miscarriages. The other three pregnancies in the investigational groups resulted in live births with no reported complications. None of the pregnant subjects had antibody responses to rhBMP-2 or Type I collagen (bovine or human), that were detectable to the limits of the sensitivity of the assay.

Two cases of cancer were diagnosed during the course of the pivotal study – one in an investigational group and one in the control group. An investigational subject was found to have pancreatic cancer while a control subject was found to have breast cancer. No additional information is available on these subjects, *e.g.*, BMP-2 receptor expression.

HOW SUPPLIED

InFUSE™ Bone Graft component is supplied in three kit sizes containing all the components necessary to prepare this portion of the device, *i.e.*, the collagen sponge(s), a vial with the lyophilized growth factor, a vial with sterile water for reconstituting the growth factor, syringes and needles. The LT-CAGE™ Lumbar

Tapered Fusion Device component is supplied in seven sizes which must be properly selected based on a specific patient's anatomy.

STORAGE CONDITIONS

Store the InFUSE™ Bone Graft component at room temperature (15 – 25 degrees Centigrade (59 to 77° F)). The LT-CAGE™ Lumbar Tapered Fusion Device component should also be stored at room temperature.

DOSAGE AND ADMINISTRATION

InFUSE™ Bone Graft component is prepared immediately prior to use from a kit containing all necessary components. Once prepared, the InFUSE™ Bone Graft component contains rhBMP-2 at a concentration of 1.5 mg/mL.

The size of the InFUSE™ Bone Graft component kit and the volume of InFUSE™ Bone Graft component to be implanted are determined by the internal volume of the LT-CAGE™ Lumbar Tapered Fusion Device components which are utilized. The patient's anatomy will determine the size of the LT-CAGE™ components to be used. The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device surgical technique provides more information on templating to determine the appropriate size LT-CAGE™ Lumbar Tapered Fusion Device component.

DIRECTIONS FOR USE

InFUSE™ Bone Graft component is prepared at the time of surgery in the surgical suite by reconstituting the lyophilized rhBMP-2 with sterile water (See Instructions for Preparation), and then uniformly applying the reconstituted rhBMP-2 solution to the ACS. The InFUSE™ Bone Graft component is then inserted into the LT-CAGE™ Lumbar Tapered Fusion Device component. The complete device is then implanted through an anterior open or laparoscopic surgical approach (See the Surgical Technique manual). If the InFUSE™ Bone Graft component is not used within two hours after reconstitution, it must be discarded.

The InFUSE™ Bone Graft component must not be sterilized by the hospital. The LT-CAGE™ Lumbar Tapered Fusion Device component, if not supplied sterile, should be sterilized before insertion of the InFUSE™ Bone Graft component. Refer to the package insert for the LT-CAGE™ Lumbar Tapered Fusion Device component for information on packaging, cleaning/decontamination and sterilization of this component and its instruments.

PRODUCT COMPLAINTS:

Any health care professional (e.g., customer or user of this system of products), who has any complaints or who has experienced any dissatisfaction in the quality, identification, durability, reliability, safety, effectiveness and/or performance of this product, should notify the distributor, Medtronic Sofamor Danek. Further, if any of the

implanted InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device components ever "malfunction," (i.e., do not meet any of their performance specifications or otherwise do not perform as intended), or are suspected of doing so, the distributor should be notified immediately (1-800-933-2635). If any Medtronic Sofamor Danek product ever "malfunctions" and may have caused or contributed to the death or serious injury of a patient, the distributor should be notified immediately by telephone, fax or written correspondence. When filing a complaint, please provide the component name and number, lot number, your name and address, the nature of the complaint and notification of whether a written report from the distributor is requested.

DEVICE RETRIEVAL EFFORTS:

Should it be necessary to remove an InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device, please call Medtronic Sofamor Danek prior to the scheduled surgery to receive instructions regarding data collection, including histopathological, mechanical and adverse event information.

IN USA

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Posterior lumbar interbody fusion using recombinant human bone morphogenetic protein type 2 with cylindrical interbody cages

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Abstract

BACKGROUND CONTEXT: In a large series of human patients undergoing open anterior lumbar interbody fusion with a tapered titanium fusion cage, recombinant human bone morphogenetic protein type 2 (rhBMP-2) on an absorbable collagen sponge carrier has been shown to decrease operative time and blood loss, to promote osteoinduction and fusion and to be a safe and effective substitute for iliac crest harvesting.

PURPOSE: The purpose of the study was to determine the clinical and radiographic outcomes in patients treated for single-level degenerative lumbar disc disease with a posterior interbody fusion, using stand-alone cylindrical threaded titanium fusion cages with either autogenous bone graft or rhBMP-2 and an absorbable collagen sponge carrier.

STUDY DESIGN/SETTING: A prospective, randomized, nonblinded, 2-year pilot study at 14 investigational sites.

PATIENT SAMPLE: Between March 1999 and December 1999, 67 patients with symptomatic, single-level degenerative lumbar disc disease of at least 6 months' duration underwent a single-level posterior lumbar interbody fusion using two paired cylindrical threaded titanium fusion devices. Patients were randomly assigned to one of two groups: one (n=34 patients) received rhBMP-2 on a collagen sponge carrier; the other (n=33 patients) autogenous iliac crest bone graft.

OUTCOME MEASURES: Clinical outcomes were measured using low back and leg pain numerical rating scales, the Short Form (SF)–36, Oswestry Low Back Pain Disability Questionnaire and work status. Plain radiographs and computed tomographic scans were used to evaluate fusion at 6, 12 and 24 months after surgery.

METHODS: In this prospective nonblinded study, 67 patients were randomly assigned to one of two groups who underwent interbody fusion using two cylindrical threaded fusion cages: the investigational group (34 patients), who received rhBMP-2 on an absorbable collagen sponge, and a control group (33 patients), who received autogenous iliac crest bone graft. Clinical data were collected and analyzed by a commercial entity.

RESULTS: The mean operative time and blood loss for the investigational rhBMP-2 group was 2.6 hours and 322.8 ml, respectively. For the autograft control group, these values were 3.0 hours and 372.7 ml. The differences were not significant. Although not statistically different, at 24 months, the investigational group's fusion rate of 92.3% was higher than the control's at 77.8%. At all postoperative intervals, the mean Oswestry, back and leg pain scores and physical components of the SF-36 improved in both treatment groups compared with preoperative scores, but no significant differences were found between groups. A statistically significant difference in the change in back

FDA device/drug status: not approved for this indication (rhBMP-2 and INTER FIX device).

Authors JKB, CLB and RWH (consultants for Medtronic Sofamor Danek) and RWH (stockholder for Medtronic Sofamor Danek) acknowledge a financial relationship that may indirectly relate to the subject of this research.

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pain was found at 24 months for the investigational group. In the control group, two adverse events related to harvesting of the iliac crest graft occurred in two patients (6.1%).
CONCLUSIONS: This small multicenter, randomized, nonblinded trial showed few statistically significant differences between the study groups. Both groups showed comparable improvements on outcome scores. Overall results show that the use of rhBMP-2 can eliminate the need for harvesting iliac crest graft and may be an equivalent replacement for autograft for use in successful posterior lumbar interbody fusions. Further studies of the use of rhBMP-2 in posterior lumbar interbody fusion cage procedures are needed.

Keywords: Posterior lumbar interbody fusion; Bone morphogenetic protein; Osteoinduction; Radiography; Interbody fusion cages

Introduction

Posterior lumbar interbody fusion (PLIF) is an effective treatment for patients with symptomatic degenerative disc disease, spondylolisthesis and other painful discogenic syndromes. Fusion of the degenerative and unstable lumbar spinal motion segment can give significant relief from this disabling and often progressive condition [1–4]. PLIF limits the extent of posterolateral soft tissue exposure, muscle stripping and injury. With this technique, the surgeon uses the traditional posterior approach to the lumbar spine; however, dissection is limited laterally to the facet joints. Through this approach, direct neural decompression can be completed, disc space height and sagittal balance can be restored [2–6] and intervertebral grafts can be placed in a biomechanically advantageous position.

Lumbar spine stabilization procedures that limit the extent of posterior spinal muscle exposure have some significant advantages. With PLIF surgical techniques, the fusion bed is within the disc space, which eliminates the exposure of the transverse processes. The PLIF approach to the lumbosacral spine enables the surgeon to reestablish the normal anatomic alignment and the relationships of the spinal motion segment while avoiding excessive injury to the posterior paravertebral muscles [2–6].

Cloward [1] presented his technique for this innovative procedure in 1953. In his surgical technique, he described using a wide laminectomy and facetectomies that would allow for the placement of large structural bone grafts in the denuded and meticulously prepared disc space. Later, Lin et al. [2] modified this intervertebral grafting technique of structural grafts. This modified PLIF technique involves filling the disc space with cancellous bone strips, allowing for preservation of a portion of the posterior elements and avoiding the complication of insertion of large structural grafts. Additional modifications of the bone graft technique and bone graft materials have been made. Kuslich et al. [3] and Ray [4] introduced the idea of using threaded interbody fusion cages inserted through a PLIF approach as a means of stabilizing the lumbar motion segment, increasing rates of fusion and improving clinical outcomes.

Recombinant human bone morphogenetic protein type 2 (rhBMP-2) [7] applied to an absorbable collagen sponge carrier has been shown to promote osteoinduction and fusion in the lumbar spine [8–11]. In a large series of patients who underwent stand-alone anterior lumbar interbody fusion with fusion cages, rhBMP-2 was shown to enhance rates of fusion, reduce surgical time and improve clinical outcomes [12,13]. To further evaluate this method of bone graft replacement, we evaluated the clinical and radiographic outcomes at 24 months of 67 patients who underwent a single-level PLIF. We compared the outcomes in the investigational patients (rhBMP-2) with those in the control patients (autogenous bone).

Materials and methods

Study design

Between March 1999 and December 1999, 67 patients with degenerative disc disease underwent surgery in this prospective, randomized, nonblinded, FDA-approved study at 14 investigational sites. Although investigators originally planned to enter hundreds of patients into the study, some of the preliminary computed tomography (CT) scans at 6 months of the initial patients revealed bone posterior to the PLIF cages [14,15]. Out of abundant caution, investigators suspended enrollment. By the time it was determined that the radiographic findings did not affect clinical outcome, the use of stand-alone PLIF cages had gone out of favor, and the study was not restarted.

All sites had local investigational review board approval, and the patients entered into the study gave their informed consent. All patients underwent a single-level PLIF with two paired INTER FIX devices (Medtronic Sofamor Danek, Memphis, TN). The interbody fusion cages were used as stand-alone construct in the disc space from L2 to S1, with the majority being at the L4–L5 level. Patients were randomly assigned in a 1:1 manner to one of two groups: the investigational group, who received rhBMP-2 on an absorbable collagen sponge carrier, and the control group, who received autogenous iliac crest bone graft taken from the posterior approach. INFUSE Bone Graft (Medtronic Sofamor Danek, Memphis, TN) is the trademarked name for rhBMP-2 applied to an absorbable collagen sponge.

Patient data

Preoperatively, all patients had symptomatic, single-level degenerative lumbar disc disease and symptoms of disabling

low back or leg pain, or both, of at least 6 months' duration that had not responded to nonoperative treatment. Patients could also have up to Grade I spondylolisthesis. The investigational, or rhBMP-2, group comprised 34 patients, and the control group comprised 33 patients. The two treatment groups were similar demographically (Table 1). No statistically significant differences ($p<.05$) were found for any of the preoperative variables.

Clinical and radiographic outcome measurements

Patient assessments were completed preoperatively, during hospitalization and postoperatively at 6 weeks and at 3, 6, 12 and 24 months. Clinical outcomes were assessed using back, leg and graft-site pain questionnaires, Short Form (SF)–36, Oswestry Low Back Pain Disability Questionnaire and work status. Back and leg symptoms were assessed separately on a visual analog scale. The intensity of pain and the duration of pain in back and leg symptoms were measured on a 10-point numeric rating scale. Adding the numeric rating scores for pain intensity and pain duration allowed examiners to derive a composite back and leg pain score, which ranged from 0 (no pain) to 20 (maximum pain).

Radiographs and CT scans were used to evaluate fusion at 6, 12 and 24 months after surgery [16]. Standing lateral and flexion-extension lateral radiographic views were obtained at each follow-up interval. Thin-cut 1-mm CT scans were taken at 6, 12 and 24 months. Two independent, blinded radiologists interpreted all radiographs and CT scans. A third independent, blinded radiologist was used to adjudicate conflicting fusion findings. Fusion was defined as an absence of radiolucent lines covering more than 50% of either implant, translation of 3 mm or less and angulation of less than 5 degrees on flexion-extension radiographs, and continuous bone growth connecting the vertebral bodies. Patients who had secondary surgeries because of persistent low back symptoms and clinically suspected nonunions were considered as having failed fusions and were classified as failures in all fusion calculations, regardless of their independent radiologic assessment.

Table 1
Patient demographic information

Variable	Investigational (n=34)	Control (n=33)	P Value*
Age (years), mean (range)	46.3 (25.8–66.1)	46.1 (28.5–70.9)	.928
Weight (pounds), mean ± SD	180.5 ± 38.4	172.8±35.7	.400
Sex, n (%)			
Male	17 (50)	15 (45.5)	.808
Female	17 (50)	18 (54.5)	
Workers' compensation, n (%)	8 (23.5)	9 (27.3)	.784
Spinal litigation, n (%)	3 (8.8)	1 (3.0)	.614
Tobacco use, n (%)	18 (52.9)	15 (45.5)	.628
Alcohol use, n (%)	15 (44.1)	9 (27.3)	.204
Preoperative work status, n (%) working	9 (26.5)	15 (45.5)	.131
Previous back surgery, n (%)	12 (35.3)	13 (39.4)	.803

*For continuous variables, p values are from analysis of variance, and for categorical variables, they are from Fisher's exact test.

Clinical and radiographic follow-up

The rate of patient return for follow-up was at least 89.6% at all postoperative periods. At 12 months, the rate of patient return for both treatment groups was at least 90%. At 24 months, the follow-up rate for the investigational group was 89.6% and the control group's rate was 100%.

Surgical technique

An open posterior interbody fusion procedure was carried out in each patient. Preoperatively, the patient's disc space was templated to determine the appropriate intraoperative disc space distraction and cage size. Plain radiographs were assessed to determine normal disc space height of the adjacent spinal motion segments. Axial CT scans or magnetic resonance images were used to establish the anterior-posterior and the transverse dimensions of the disc space to ensure proper cage sizing.

The patient was placed in the prone position on padded bolsters that support the chest and pelvis and suspend the abdomen. Care was taken to extend the pelvis to ensure that lumbar lordosis was preserved. The operating room table accommodated plain radiographs or fluoroscopy.

A complete laminectomy with facetectomies or extensive bilateral laminotomies and facetectomies with preservation of the midline elements was performed in each patient. The lateral borders of the disc were exposed along with the traversing and exiting nerve roots. Bilateral annulotomies were made, and a complete discectomy was carried through these annular windows. The annulotomies were placed lateral to the dural tube. The mid-portion of the lateral annular window was centered adjacent to the medial wall of the pedicle. The anterior and lateral walls of the annulus were preserved; the entire nucleus was removed. Cartilaginous end plates were resected using curettes; the bony end plates were preserved.

Reduction of sagittal and frontal plane deformities was achieved through disc space height restoration and annular tensioning. Inserting progressively larger dilators into the collapsed disc restored disc space height and the normal sagittal contours of the spine.

The vertebral end plates were prepared with reamers that uniformly cut a channel through the adjacent bony end plates. Great care was taken to visualize and gently retract both the traversing and exiting nerve roots. Before reaming, a tubular reamer guide that was impacted into the disc space protected these soft tissue elements. Care was taken to ensure that the end plate cuts were made parallel and equally into each end plate.

The INTER FIX cages were filled with either the appropriately sized rhBMP-2–soaked sponges or morcellized autograft before they were inserted. The cages were inserted sequentially in the disc space and away from any soft tissue or neural elements. Their position was assessed intraoperatively with plain radiographs or fluoroscopy. However, cages were not routinely recessed within the disc space as determined by postoperative CT scans. The majority of the cages were left flush to the posterior cortical wall of the vertebral bodies; some cages remained partially within the spinal canal or neuroforamina.

Iliac crest bone graft harvesting

The control group received autogenous iliac crest graft placed within the cages. The bone graft was harvested from the outer table of the iliac wing. The graft was morcellized using a rongeur and was tightly packed into the cages before their insertion.

RhBMP-2 preparation

The rhBMP-2 was reconstituted using sterile water and was used as a single dose of 1.5 mg/ml in all study patients. The 1.5-mg rhBMP-2/ml solution was applied to an absorbable collagen sponge and allowed to bind to the sponge for a minimum of 15 minutes. The dose of rhBMP-2 varied by patient depending on cage size, with the total dose ranging from 4.0 mg to 8.0 mg. The rhBMP-2–soaked sponge was then placed in the hollow central portion of the INTER FIX device before its insertion into the prepared disc space. No additional sponges were placed outside of the devices. No autogenous grafts were used in the investigational group.

Postoperatively, patients were placed in a soft lumbar corset. The treating physician decided when the patient would advance in activities. Isometric strengthening and exercise programs were started at 6 weeks after surgery.

Statistical methods

The data from this clinical trial were analyzed using the statistical software package SAS version 6.12. For comparisons between the groups for continuous variables, p values are from analysis of variance, and for categorical variables, they are from Fisher's exact tests or chi-squared tests. For changes (improvements) from the preoperative within each group, the p values are from paired *t* tests.

Results

Surgery

The mean operative time, average blood loss and average hospital stay were less for the investigational group than for the control group (Table 2). None of these differences between treatment groups was statistically significant, although the time of surgery approached significance (p=.065). No unanticipated device-related adverse events occurred in either treatment group.

Table 2
Surgical parameters

Variable	Investigational group	Control group
Mean operative time	2.6 hours	3.0 hours
Average blood loss	322.8 ml	372.7 ml
Average hospital stay	3.4 days	5.2 days

Vascular complications

One control patient developed deep venous thrombosis and was treated with anticoagulation medications.

Neurological complications

Three investigational (8.8%) and 2 control patients (6.1%) had dural tears. With regard to neurological complications in our study patients, 16 events occurred in 14 investigational patients and 18 events occurred in 14 control patients.

Iliac crest graft site complications

In the control group, adverse events related to harvesting of the iliac crest graft were identified in two patients (6.1%). These events included one case of pain and one hematoma. Neither of these patients required additional surgery. Obviously, no graft site adverse events occurred in the investigational group because the use of rhBMP-2 precluded the need to harvest bone graft.

The level of postoperative pain and morbidity associated with the iliac crest graft harvesting was measured using numeric rating scales for pain intensity and duration (Fig. 1). After surgery, all of the control patients experienced hip donor site pain. The highest levels of pain were noted immediately after surgery with a mean score of 11.6 points of 20 points. The percentage of patients experiencing pain decreased over time; however, at 24 months after surgery, 60% of the control patients still experienced pain (ie, had scores greater than 0). At 2 years, the graft site pain scores averaged 5.5 points of 20 and 13.3% of the patients still felt that the appearance of the graft site bothered them some.

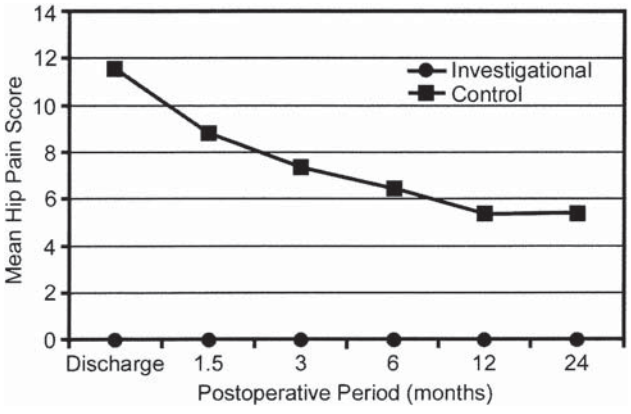

Fig. 1. Mean hip pain scores.

Antibody testing

Antibodies to rhBMP-2, bovine Type I collagen and human Type I collagen were evaluated preoperatively and 3 months postoperatively using enzyme-linked immunosorbent assays (ELISAs). None of the patients in either group tested positive for antibodies to rhBMP-2 or human Type I collagen. Authentic (greater than 3 times baseline) bovine Type I collagen antibody formation occurred in three investigational and five control patients. GELFOAM sponge was used in 15 of the 34 investigational patients (44%). Of these 15, 2 developed antibody formations to bovine collagen. GELFOAM sponge was also used in 20 of 33 (61%) of the controls. Of these 20, 7 had antibody formation to the bovine collagen. Of the 3 investigational patients who had elevated antibodies, only 1 had GELFOAM sponge used, and of the 5 control patients who had bovine collagen antibodies, only 2 had GELFOAM sponge used. Thus, there was no obvious correlation between GELFOAM sponge use and antibody formation. No negative clinical consequence to the positive bovine collagen antibody test results was evident in any of the patients; and the fact that the bovine antibody response occurred as often in the investigational group as in the control shows that the bovine collagen sponge used to deliver the rhBMP-2 was not the cause of the antibody reaction. A similar result was found when the same carrier and dose of rhBMP-2 were used inside cages implanted anteriorly [9,12].

Clinical outcomes

Oswestry Disability Questionnaire scores

The Oswestry Low Back Pain Disability Questionnaire measured pain associated with activities. The Oswestry Questionnaire was administered preoperatively as well as at each postoperative visit. At all postoperative visits, both treatment groups demonstrated highly significant improvements as compared with the preoperative scores (Fig. 2). At all postoperative time intervals after the first 6-week follow-up period, the investigational group showed greater improvements over the control group in mean overall Oswestry scores. At last follow-up at 24 months, the mean improvements in the Oswestry scores were 29.6 points in the investigational group and 24.9 points in the controls. In the investigational group, 69% of patients showed an improvement of at least 15 points in their disability scores at 12 months after surgery as compared with 55.6% of patients in the control group. At 24 months, the 76.0% of the investigational group was improved and compared favorably with 64.3% improved in the control group (Table 3).

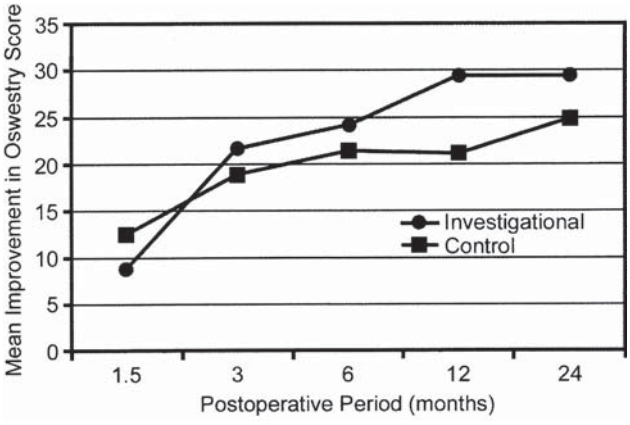

Fig. 2. Mean improvement in Oswestry scores.

Back pain

The mean back pain scores at all postoperative periods were improved from the preoperative mean values for both treatment groups (Fig. 3). The mean improvements in back pain scores at all five postoperative intervals studied were greater for the investigational group than for the control autograft group (Fig. 4). At 24 months, the average improvement in back pain in the investigational group was almost twice that of the control group (9-point improvement vs 4.5-point improvement). This difference was highly significant with a p value of .009.

Leg pain

Leg pain was assessed in a similar manner using a 20-point numeric rating scale that reflects both the intensity and duration of painful symptoms. Mean leg pain scores improved significantly after surgery in each group (Fig. 5). At each study interval, average leg pain scores were less (better) in the investigational group when compared with the control group. Similarly, the investigational group also showed higher average improvement scores at each interval studied. At 24 months, the average improvement in leg pain was 7.7 points in the investigational group compared with 6.5 points in the control group. This difference was not statistically significant.

Table 3
Twenty-four month clinical outcome parameters

	Investigational	Control
Improvement points in Oswestry score	29.6	24.9
Percentage of patients with ≥15 point Oswestry improvement	69%	55.6%
Percentage of patients with Oswestry improvement	76.0%	64.3%
Back pain improvement from before surgery (points)	9*	4.5
Leg pain average improvement from before surgery (points)	7.7	6.5
Motor change from before surgery	4.5	2.8
Sensory change from before surgery	8.0	2.8
Reflex change from before surgery	7.0	5.4
Straight leg raise change from before surgery	48.0	39.3
Net change in percentage of patients working	+8.8%	−3.1%
Median return to work time	43 days	137 days
Fusion rate	97.3%	77.8%

*Statistically significant difference ($p<.05$)

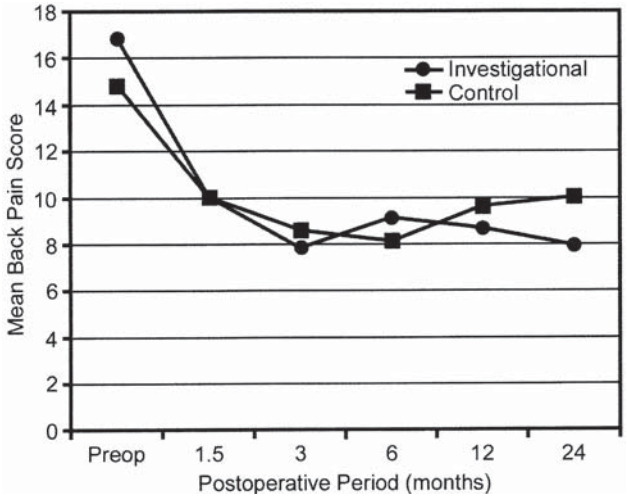

Fig. 3. Mean back pain scores.

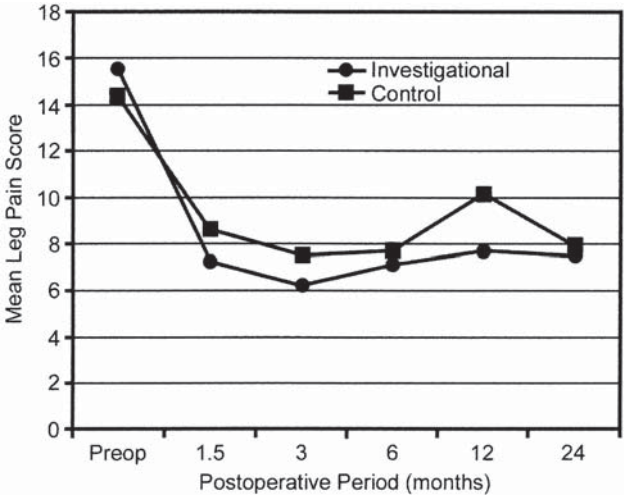

Fig. 5. Mean leg pain scores.

Short Form–36

At all postoperative follow-up intervals, the investigational group showed greater improvement in the physical component score of the SF-36 when compared with the controls (Fig. 6).

Neurological status

Preoperatively and at all five postoperative time points, the motor, sensory, reflexes and straight-leg-raise measurements were essentially the same for both treatment groups and showed no statistical differences. At 24 months, using the protocol criteria for determining overall neurological success, which represents a combination of the four neurological measurements, both groups had 100% success. Table 3 contains the change from preoperative results at 24 months for the motor, sensory, reflex and straight-leg-raise measurements.

Work status

Many factors affect a patient's work status, such as the nature of the work performed and ability of the workplace to accommodate work restrictions. Before surgery, only 26.5% of the investigational group was employed, whereas more than 45.5% of the control patients were employed (Table 3). For patients who were working before surgery, the median return-to-work interval was 43 days in the investigational group and 137 days in the control group. Although marked, this difference was not statistically significant. At last follow-up, more people in the investigational treatment group were working than were working before their surgery. At 2 years after surgery, 12 patients in the investigational group were employed, whereas only 9 were employed before surgery. In the control group, 15 were working before surgery and 14 were working at 2 years after surgery. In other words, the percent of the investigational patients working went from 26.5% before surgery to 35.3% at 2 years, whereas in the

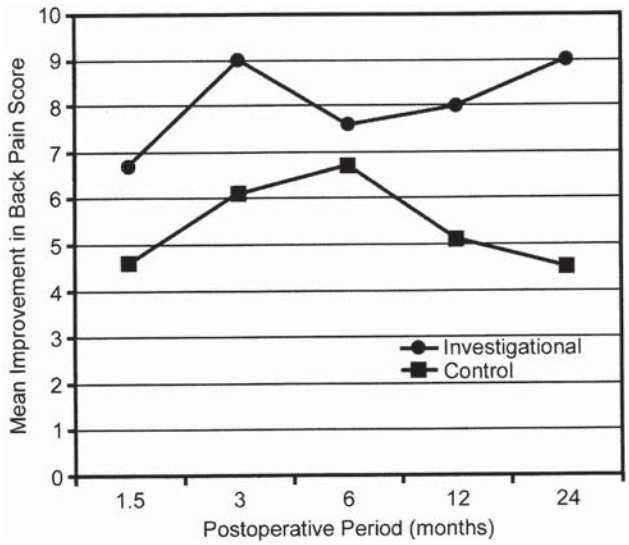

Fig. 4. Mean improvement in back pain scores.

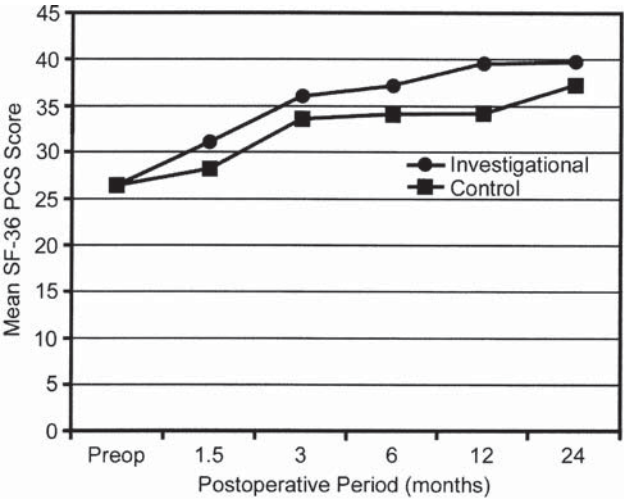

Fig. 6. Mean Short Form (SF)–36 physical component scores (PCS).

control group the rate went from 45.5% to 42.4%. Although none of these changes is statistically significant, the trend may reflect the statistically significant difference of lower back pain in the investigational patients.

Patient satisfaction

At 12 and 24 months after surgery, the results were similar in each treatment group (Table 4). At 24 months, 72.4% of the investigational patients and 80.0% of the control patients were satisfied (answering definitely true or mostly true) with their surgical outcomes. In the investigational group, 69.0% said they would undergo surgery again (answering definitely true or mostly true) compared with 83.3% of the control patients who would undergo surgery again. In the investigational group, 72.4% believed that they were helped as much as they had expected to be from the surgery; 70.0% of the control group felt they had been. None of these subjective differences was statistically significant.

Radiographic outcomes

Cage placement

Cage placement was assessed on both plain radiographs and thin-cut CT scan. The CT scans were found to reflect more accurately the position of the cage in relation to the spinal canal posteriorly and neuroforamina laterally. No differences between the two patient groups regarding cage placement were detected. Only 6% of patients in each group (2 of 34 in the investigational group; 2 of 33 in the control group) showed cages that were countersunk 3 mm or more from the posterior margin of the vertebral body. Approximately one-third of patients in each group had cages that marginally extended into the spinal canal or neuroforamina on postoperative CT studies (12 of 34 in the investigational group; 10 of 33 in the control group). The remainder of the cages were placed either flush to the posterior cortex of the vertebral bodies or were recessed by only 2 mm or less.

Table 4
Summary of patient satisfaction with results of surgery at 24 months

Variable	Investigational patients, n (%)	Control patients, n (%)	p Value*
I was satisfied with the results of my surgery			
Definitely true	15 (51.7)	16 (53.3)	.388
Mostly true	6 (20.7)	8 (26.7)	
Do not know	3 (10.3)	5 (16.7)	
Mostly false	3 (10.3)	0 (0.0)	
Definitely false	2 (6.9)	1 (3.3)	
I was helped as much as I thought I would be by my surgery			
Definitely true	13 (44.8)	16 (53.3)	.159
Mostly true	8 (27.6)	5 (16.7)	
Do not know	3 (10.3)	8 (26.7)	
Mostly false	3 (10.3)	0 (0.0)	
Definitely false	2 (6.9)	1 (3.3)	
All things considered, I would have the surgery again for the same condition			
Definitely true	18 (62.1)	16 (53.3)	.196
Mostly true	2 (6.9)	9 (30.0)	
Do not know	5 (17.2)	2 (6.7)	
Mostly false	1 (3.4)	1 (3.3)	
Definitely false	3 (10.3)	2 (6.7)	

*p values are from the chi-square test.

Sagittal plane balance

Nearly one-third of the patients (20 of 67; 30%) had some sagittal plane imbalance before surgery. At their last follow-up, six patients had some residual spondylolisthesis from failure to fully reduce the deformity at the time of surgery (up to Grade I spondylolisthesis was allowed), and two patients developed spondylolisthesis after surgery. Eleven patients had residual retrolithesis after surgery.

Intradiscal bone formation

Fusion status of the study patients was independently evaluated on plain radiographs and CT scans. At 6 months after surgery, 93.1% of patients in both the investigational and control groups had evidence of fusion. At 12 months, the fusion rate in the investigational group decreased to 85.2%, whereas the control group maintained a fusion rate of 92%. This decrease in fusion rate in the investigational group at 12 months appears to be artificially low because seven patients who were evaluated at 24 months could not be evaluated at 12 months because of the unavailability of reconstructed CT views or poor-quality films. At 24 months, the investigational group had a 92.3% fusion rate, which was more than 14 percentage points higher than that of the control group (77.8%). This difference was not statistically significant.

Bone formation outside the disc space

Thin-cut 1-mm CT scans and plain radiographs were used by multiple reviewers to examine for new bone formation adjacent to the interbody fusion cages in 32 of 34 investigational patients and 31 of 33 controls. (Scans or radiographs were unavailable in four patients because they were either not taken or were of quality that was too poor to read.). New bone formation extending outside the disc space and into the spinal canal or neuroforamina was found in 28 patients (24 investigational and 4 control group patients). According to Fisher's exact test, this difference is statistically significant ($p<.0001$). Despite the statistical difference, this unexpected posterior bone formation was not correlated to a recurrence or increase in leg pain from the preoperative state. In 10 (29%) investigational and 12 (36%) control patients, the leg pain at some point in the follow-up increased at least 1 point (on a 20-point scale) over the preoperative value (Table 5). Interestingly, 7 of the 22 control patients with increased leg pain had absolutely no bone formation outside of the disc space. This last finding suggests that bone formation extending outside of the disc space is not the only possible explanation of recurrent leg pain.

Table 5
Posterior lumbar interbody fusion patients with bone formation and leg pain increase

	Investigational (n=32)		Control (n=31)	
Bone formation score*	Patients with bone formation only (n)	Patients with bone formation and leg pain increase (n)	Patients with bone formation only (n)	Patients with bone formation and leg pain increase (n)
0	2	0	22	7
1	6	2	5	1
2	14	5	4	2
3a	3	1	0	0
3b	3	1	0	0
3c	4	1	0	0
Films not read	2	0	2	2
Total	34	10	33	12

*Bone formation score based on grading system by Alexander and Branch [15]: 3a=posterior bone formation extending centrally into the spinal canal; 3b=posterolateral bone formation extending into the neuroforamina; 3c=posterior and posterolateral bone formation.

Sagittal plane balance

In the control group, two of the four patients (50%) with bone in the spinal canal had a residual unreduced spondylolisthesis after surgery. New bone formation was commonly identified in the canal posterior to the unreduced superior vertebra under the posterior longitudinal ligament and annulus. In two of four patients (50%) with normal segmental sagittal plane balance in the control group, new bone formation was identified extending into the spinal canal.

In the investigational group, 12 of the 24 patients (50%) with bone in the spinal canal had some residual postoperative sagittal plane imbalance. Six of 24 patients (25%) had spondylolisthesis and 6 of 24 (25%) had retrolisthesis. In each of these patients, new bone formation commonly occurred posterior to the unreduced vertebral body under the posterior longitudinal ligament lifted off the unreduced vertebral body. Twelve of 32 patients in the investigational group (38%) had a normal postoperative segmental sagittal plane balance and new bone formation in the spinal canal.

Cage placement

In the investigational group, cage placement was strongly associated with the development of bone in the spinal canal. In the investigational group, 23 of 30 patients (77%) with cages placed at the margin or within 2 mm of the margin of the posterior vertebral cortex developed some bone in the spinal canal. Only six investigational patients with prominently placed cages did not exhibit posterior bone growth. Twelve percent of patients in the control group whose cages were placed within 2 mm of the vertebral margins developed bone in the spinal canal. No patient in either group whose cage had been recessed by 3 mm or more developed bone in the spinal canal.

Secondary surgical procedures

In the investigational group, 6 of 34 (17.6%) had some type of secondary spinal surgical procedure. Three (8.8%) were classified as failures because they had undergone a second spinal surgery at the same level but were not considered radiographic fusion failures. Three additional patients underwent a spinal fusion procedure at a different spinal level. In the control group, 6 of 33 patients (18.2%) had some type of secondary spinal surgical procedure. Three (9.1%) had second spinal surgery for fusion failures. Three others (9.1%) had second spinal surgeries at a different spinal level.

Discussion

Threaded cylindrical cages represent a new, distinct class of segmental spinal fixation devices. These devices were not designed as spacers that require segmental stabilization; rather, they were designed as stand-alone intervertebral devices that function as an "instrumented PLIF." Threaded interbody devices are biomechanically different from interbody spacers. Biomechanical studies have shown that cage size has some significance in stand-alone cage fusions; however, stand-alone cages do not significantly increase spinal stiffness in studies using human cadavers [5,17–21]. This finding largely explains the current clinical trend toward using posterior segmental fixation in PLIF constructs.

Larger cages improve stiffness in rotation and lateral bending in a lumbar spinal motion segment; however, reduction of motion in flexion is not significantly improved with larger cages [19,20]. Larger cages require more extensive facet joint resection or complete facetectomy, which further destabilizes the spinal motion segment. A cylindrical device increases in its medial-lateral dimension equal to its increase in height, which necessitates greater mobilization and retraction of the neural elements. Retraction and mobilization of the neural element during cylindrical cage insertion has been associated with permanent neurologic injury [22,23]. The current trend in PLIF surgery is to limit neural element retraction through the use of a transforaminal surgical approach or through the use of impacted interbody spacers.

Initial clinical studies reported high rates of fusion and clinical success in certain centers. These results have not been widely reproduced. Authors of clinical and radiographic studies on stand-alone interbody implants without supplemental fixation have reported fusion rates between 83% and 100% [3,4]. Hacker [24] compared two groups of patients treated for disabling back pain; one group was treated with a stand-alone PLIF using Bagby and Kuslich (BAK) implants, and the other group was treated with combined anteroposterior fusion. He found equal patient satisfaction between the two groups. Ray [4] presented a prospective series of 236 patients treated with stand-alone interbody

fusion and reported a 96% fusion rate at 2 years after surgery. These fusion criteria did correlate with improved clinical outcomes. In this study group, only 65% had good-to-excellent clinical outcomes on the Prolo scale, and 14% had a poor result.

However, PLIF procedures, or any other type of spinal fusion procedure that uses autograft from the iliac crest, come with a price in pain for the patient. Figure 1 shows that the iliac crest graft site pain in this study was found to be similar to that measured in the same way for a larger study on anterior lumbar interbody fusion (ALIF) procedures [12] with two exceptions. First, in this study, the average pain at 24 months was 5.5 on a scale of 20, whereas in the anterior fusion study, the average pain score was 1.8. Second, in this PLIF study, 60% of the patients had some pain at 24 months, whereas in the ALIF study 32% had persistent pain. Although these were two separate studies using different surgeons, different numbers of patients (33 vs 134) and different volumetric sizes of cages, these results are consistent with a review of other studies that showed

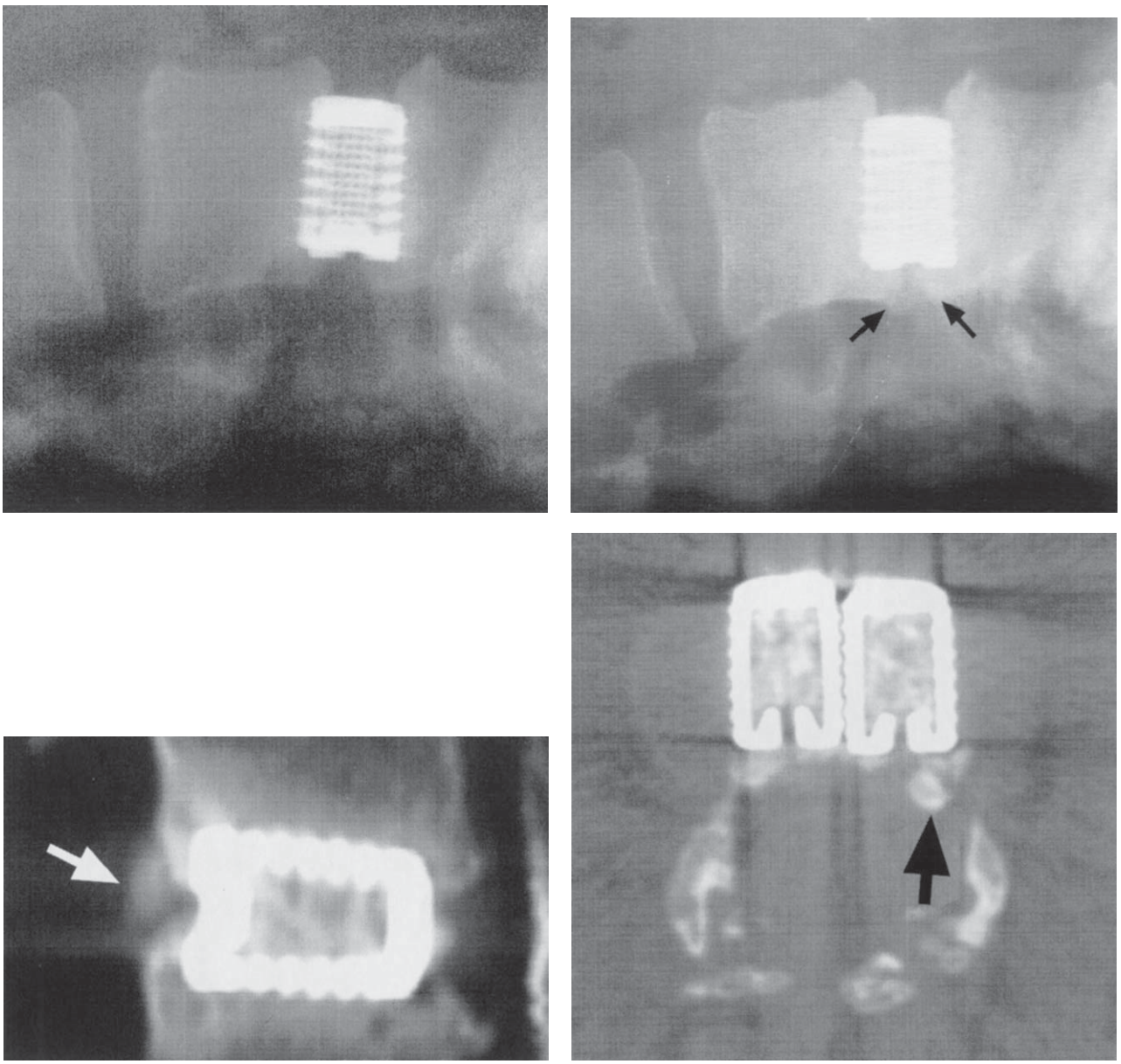

Fig. 7. (Top left) Lateral radiograph of the L3–L4 interspace 3 months after a posterior lumbar interbody fusion (PLIF) procedure using autogenous iliac bone graft. The disc space height has been restored anatomically, and the cages are recessed by 3 mm within the disc space. There is no bone posterior to the cages. (Top right) Lateral radiograph at 24 months after the PLIF with autograft shows loss of disc space height, subsidence of the implants through the vertebral end plates and new bone formation posterior to the cages (arrows). The posterior bone formation extends into the spinal canal. (Bottom left) Sagittal computed tomography (CT) scan reconstruction across the L3–L4 interspace at 20 months after the PLIF using autograft confirms that there is new bone formation posterior to the implants that extend into the spinal canal (arrow). (Bottom right) Axial CT scan across the L3–L4 interspace at 24 months after surgery shows new bone formation (arrow) extending into the spinal canal.

that a posterior approach to the iliac crest is more painful for the patients [25]. The pain associated with the posterior bone graft harvest may be secondary, in part, to the extensive stripping of the gluteus musculature, more extensive bone graft harvesting techniques or injury to the sacroiliac joint. For whatever reason, the measured iliac crest graft site pain scores in this study suggest that, from the patient's point of view, the need for an autograft replacement in posterior spinal procedures is greater than in anterior spinal fusion procedures.

We found that, regardless of the source of the bone graft, extra bone formation in the spinal canal can occur after PLIF procedures using stand-alone cylindrical interbody fusion cages because it occurred in both study groups (Fig. 7). Bone formation in the spinal canal and neuroforamina appears to be a multifactorial event. It appears to be largely dependent on cage placement and sagittal balance of the instrumented vertebral motion segment. Patients with residual sagittal plane imbalance tend to form bone behind the unreduced vertebral segment. This may be the result of lifting of a periosteal flap along the posterior cortex of the listhesed vertebral body (Fig. 8). Cages that were not recessed 3 mm or more within the confines of the disc space margins were also associated with bone formation in the spinal canal (Fig. 9). Thin-cut CT scans were essential to determine cage placement and new bone formation postoperatively.

RhBMP-2 on an absorbable collagen sponge has been shown to induce bone formation in the intervertebral disc space [9,10,12,13]. A recent study has shown that this montage in this milieu routinely produces a fusion zone extending 3 mm around the cage [26]. It is not surprising that bone may extend into the spinal canal when cages containing rhBMP-2 are not recessed 3 mm or more within the confines of the disc space.

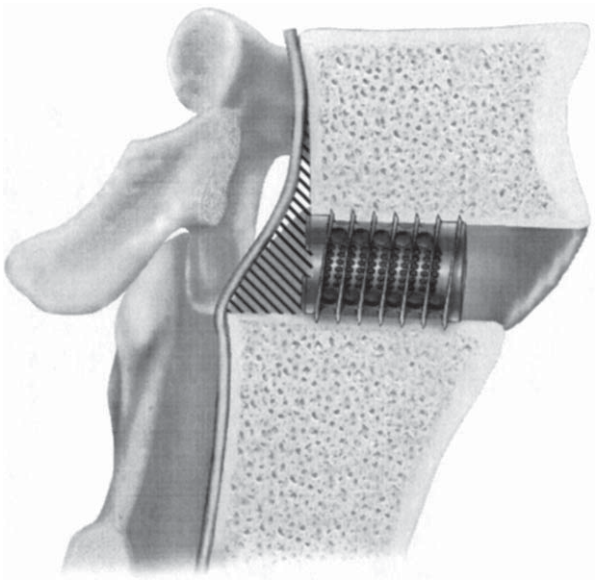

Fig. 8. Schematic illustration of an unreduced spondylolisthesis treated by a stand-alone posterior lumbar interbody fusion (PLIF) technique. There is elevation of the posterior longitudinal ligament with a triangular subperiosteal zone behind the unreduced superior vertebral body (shaded area). This zone commonly filled in with bone after the PLIF procedure in both the bone morphogenetic protein–treated and autograft-treated patients.

The PLIF procedure using threaded cylindrical fusion cages disrupts a wide channel, which includes the posterior margin of the disc, the posterior longitudinal ligament and annular structures. This injury can result in adjacent bone formation, which can extend into the spinal canal. This new bone formation is best visualized on CT scan. Both the control group and investigational group exhibited bone formation outside of the disc space after this procedure.

Although not desirable, bone formation in the spinal canal does not appear to have a discernable effect on patient outcomes. Therefore, bone formation in the spinal canal after the PLIF procedure with stand-alone cylindrical interbody fusion cages appears to be primarily just a radiographic finding that is not associated with any clinical outcome. This human study seems to confirm the safety results in a canine study using rhBMP-2 on a bovine collagen sponge [27]. In that laminectomy study, the sponge was placed directly on an exposed dura. Even though bone formed, no negative outcomes were found. In the canine and now this human study, the de novo rhBMP-formed bone occurred predictably, not compressing neural structures.

Because of its small size, this study should be considered a pilot study evaluating the ability of a bone morphogenetic protein to replace autograft in a stand-alone PLIF cage procedure. Even though the number of patients was small, we found a statistically significant improvement in back pain in the rhBMP-2 investigational patients. Although the other differences were not statistically significant, assessment of just the surgical and clinical outcome data at 2 years (Tables 2 and 3) and the averages of all of the outcomes measured (except for two of the three subjective patient satisfaction questions) favored the investigational group. In a recent 679-patient analysis, the same protein used in the same concentration inside metal cages for the same lumbar indication but from an anterior approach was shown to be superior to autograft [13]. The direction of implantation of a cage should not affect the ability of rhBMP-2 contained inside to form bone.

In conclusion, this review of the results, which represents the first use of osteoinductive proteins in a PLIF procedure, are encouraging. These findings along with other studies for other indications suggest that larger PLIF studies with rhBMP-2 are needed. In future studies using modified surgical techniques, such as using more recessed cages to allow for extra posterior bone formation, adding steps to minimize bleeding and surgical variables, using narrower, noncylindrical cages that would be easier to put in and cause less tissue destruction or adding secondary instrumentation may be beneficial. Modifying patient selection, such as entering patients with less vertebral slip, could also help minimize the confounding variables.

Readers should be advised that the use of rhBMP-2 described in this article is not approved by the US Food and Drug Administration for PLIF procedures, and the use of

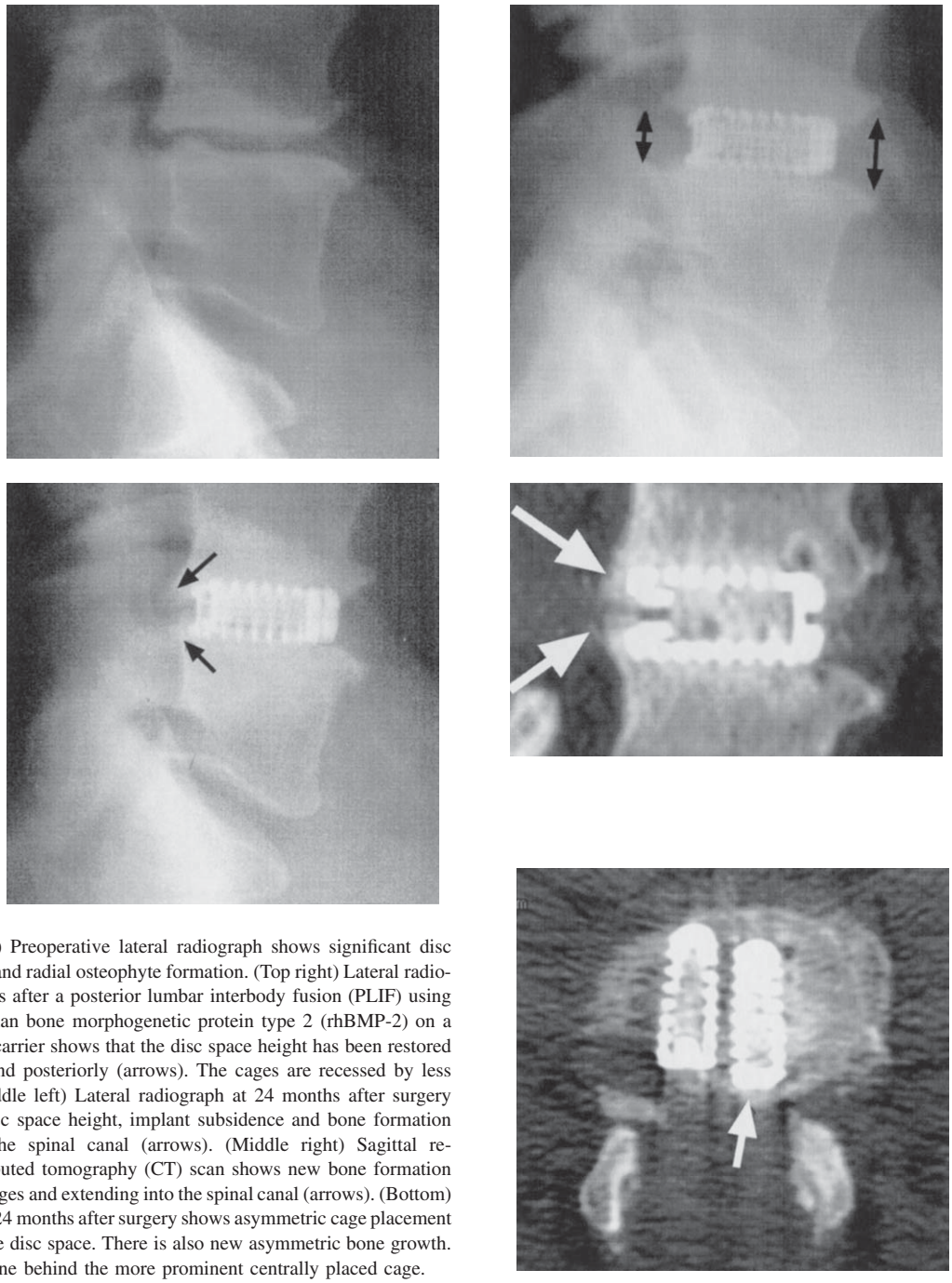

Fig. 9. (Top left) Preoperative lateral radiograph shows significant disc space narrowing and radial osteophyte formation. (Top right) Lateral radiograph at 3 months after a posterior lumbar interbody fusion (PLIF) using recombinant human bone morphogenetic protein type 2 (rhBMP-2) on a collagen sponge carrier shows that the disc space height has been restored both anteriorly and posteriorly (arrows). The cages are recessed by less than 3 mm. (Middle left) Lateral radiograph at 24 months after surgery shows loss of disc space height, implant subsidence and bone formation extending into the spinal canal (arrows). (Middle right) Sagittal reconstructed computed tomography (CT) scan shows new bone formation posterior to the cages and extending into the spinal canal (arrows). (Bottom) Axial CT scan at 24 months after surgery shows asymmetric cage placement (arrow) within the disc space. There is also new asymmetric bone growth. There is more bone behind the more prominent centrally placed cage.

rhBMP-2 as described is not recommended for the standalone method described.

Acknowledgments

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COMMENTARY

Neil Kahanovitz, MD, *Philadelphia, PA*

The development and clinical testing of new devices and technology can be an exciting experience. The mere possibility that we may be able to influence or radically change the ways in which treatments and outcomes might influence a patient's life is exhilarating. Could a new device or technology change a decades-old approach to a clinical problem? The clinical, financial and social impact of such change and development is staggering. Therefore, the importance of responsible and unbiased reporting is ever so critical when introducing a new medical device or technology.

Unfortunately, the authors of this study appear to have been overwhelmed by their enthusiasm of using recombinant human bone morphogenetic protein type 2 (rhBMP-2) and a cylindrical cage through a posterior lumbar interbody fusion (PLIF) approach. There are lengthy discussions of various trends throughout this study, which imply the superiority of rhBMP over autograft. However, one fact remains: in every clinical measure examined in this study, there were no statistically superior outcomes in the rhBMP group except one, and the clinical significance of this one statistically significant finding is unclear. The authors claimed statistical significance in the measure of back pain using a visual analog scale. However, within the time-honored Oswestry scales there was no statistical difference in postoperative back pain between the two groups. If the visual analog findings are truly of statistical importance, why was there no consistency between the two measures?

This was designed to be a large multicenter study, but when the investigators began to see bone growing into the spinal canal, "Out of abundant caution, investigators suspended enrollment." The authors fail to mention any role the US Food and Drug Administration may have had in suspending enrollment in the study. In fact, the only other statistically significant variables in the entire study were the radiographic presence of bone in the spinal canal and foramina in the rhBMP group. The authors deny that intraspinal bone formation had any clinical implications. I would suppose most surgeons would be less than enthusiastic to see

this statistically significant variable present in the majority of their patients.

The authors discuss the degree and extent of postoperative graft site pain extensively. However, when asked if they would undergo surgery again, 69% of the investigational group responded positively compared with 83% of the control patients; the very same group of patients undergoing iliac crest bone graft harvest. Much like the rest of the data, these percentages showed no statistical significance, and the clarity of their conclusions based on these trends obviously needs to be tempered.

It is easy to get caught up in the exciting possibilities of new technology and devices. But let us all beware that solid scientific data must prevail. Solid science does not reside in trends. It is dependent on statistically significant data.

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RESPONSE TO COMMENTARY

Charles L. Branch, Jr., MD

As a coauthor of this paper and a deputy editor of *The Spine Journal*, I am pleased to have the opportunity to respond to my colleague's commentary. This manuscript underwent a very critical review, and this process enhanced the quality of the final manuscript. This process also reminds all of us that the interpretation of sets of data may and will be affected by the individual bias of the interpreter. As physician scientists, we are obligated to collect and report data scientifically and accurately. We are also obliged to vigorously debate the interpretation of data in order to derive the greatest good for our patients and the advancement of medicine.

This report documents one of but a few prospective, randomized, controlled clinical trials of a spinal fusion technique. In the field of evidence-based medicine, this would be recognized as Class 1 data or evidence, of which there is a paucity in the spine fusion literature. These data were collected scientifically and accurately in a Food and Drug Administration–monitored clinical investigation supported by the device manufacturer. We believe that these are quality data that must be published and subjected to interpretation and vigorous debate.

This manuscript includes interpretation of the data by the authors. Certainly the possibility of having a substance that precludes the use of harvested iliac crest autograft and that enhances the fusion process is desirable and unquestionably biases our interpretation of the data. The fact that this substance has limited commercial availability would unquestionably stimulate interpretive bias from a competitive perspective. The analysis and debate that follows is very healthy and important.

We believe that our discussion does reflect the reality of the data. Stand-alone threaded cylindrical posterior interbody fusion cages have been recognized to have significant limitations, and this awareness in the surgeon investigator group led to the cessation of enrollment in this study. Harvesting iliac crest for graft material from a posterior approach is associated with increased pain and morbidity. The bone formation in the spinal canal in the recombinant human bone morphogenetic protein type 2 (rhBMP-2) group was statistically significant when compared with the control group, yet this appeared to have little or no impact on clinical outcome. In fact, the rhBMP-2 group had superior clinical outcome by some measures. Perhaps most important is our belief that this small series should be considered as a pilot study the encouraging but not conclusive results of which should prompt, not discourage, further studies investigating the role of rhBMP-2 in a posterior interbody fusion technique.

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Affidavit

Stephen M. West, being first duly sworn, states that he is an employee of Bachman Legal Printing, located at 733 Marquette Avenue, Suite 109, Minneapolis, MN 55402. That on **September 8, 2014**, he prepared the **Respondents' Brief,** case numbers **A14-1149, A14-1150, A14-1151, A14-1152, A14-1153 and A14-1154**, and served **2** copies of same upon the following attorney(s) or responsible person(s) by **First Class Mail postage prepaid.**

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