No. 15-15653

IN THE UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

KATHRYN MARIE JONES,
Plaintiff-Appellant,

v.

MEDTRONIC, INC., ET AL.,
Defendants-Appellees.

On Appeal from a Final Judgment of the United States District Court for the District of Arizona, Hon. Steve O. Logan

AMICUS CURIAE BRIEF OF PUBLIC CITIZEN, INC., IN SUPPORT OF PLAINTIFF-APPELLANT AND REVERSAL

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CORPORATE DISCLOSURE STATEMENT

Under Federal Rule of Appellate Procedure 26.1 & 29(c)(1), amicus curiae Public Citizen, Inc. states that it has no parent corporation and issues no stock; therefore, no publicly held corporation owns 10 percent or more of it.

TABLE OF CONTENTS

TABLE OF AUTHORITIES

CASES **Page(s)**

STATUTES

REGULATONS

MISCELLANEOUS

INTEREST OF AMICUS CURIAE[1]

Amicus curiae Public Citizen, Inc., is a non-profit organization founded in 1971, with members and supporters in all fifty states. Public Citizen has a longstanding interest in public health, including drug safety and FDA regulation, and works with Public Citizen's Health Research Group to promote research-based, system-wide changes in health care policy and to provide oversight concerning drug and medical device safety, among other things. Public Citizen and its attorneys have participated, as amicus or appellate counsel for a party, in many cases concerning the preemptive scope of FDA regulation. Public Citizen therefore has substantial experience with both the regulatory and jurisprudential background of this case.

INTRODUCTON

In *Medtronic, Inc. v. Lohr*, 518 U.S. 470 (1996), the Supreme Court held that the express preemption provision of the Medical Device Amendments to the Food, Drug, and Cosmetic Act (MDA), 21 U.S.C. § 360k(a), does not preempt state-law claims based on injuries caused by a medical device when the Food and Drug Administration (FDA) has not evaluated the device for safety and effectiveness. The Court held in *Riegel v. Medtronic, Inc.*, 552 U.S. 312 (2008), that § 360k(a) does

[1] Both parties consented to the filing of this amicus brief. No counsel for any party authored this brief in whole or part. Apart from amici curiae, no person or organization, including parties or parties' counsel, contributed money intended to fund the preparation and submission of this brief.

preempt state-law claims based on injuries caused by a medical device when the FDA has granted premarket approval based on evaluation of the device's safety and effectiveness.

This case presents a question on the border of those two cases: whether § 360k(a) preempts state-law claims for injuries caused by a medical device when the device received premarket approval for one use but the manufacturer sold it for a different use, not evaluated or approved by the FDA, and the patient suffered serious injury as a result of that conduct by the manufacturer. Under the reasoning of *Lohr* and *Riegel*, the answer to this question is no.

The court below, however, held that state-law claims arising from injuries caused by aggressive marketing for an unapproved use are preempted. The errors in the court's reasoning reflect the appellate courts' broad misapplication of *Lohr* and *Riegel*. As the United States stated in a brief recommending denial of a petition for certiorari from this Court's decision in *Stengel v. Medtronic*, 704 F.3d 1224 (9th Cir. 2012), "[t]he courts of appeals, in *every* case since *Riegel* involving a device subject to premarket approval, have dispensed with the first step of a proper Section 360k(a) preemption analysis—*i.e.,* asking whether FDA has established device-specific requirements *on the same subject as* the relevant state requirement."[2] Here, the

[2] Brief for United States as Amicus Curiae, *Medtronic, Inc. v. Stengel*, No. 12-1351, at 15 (U.S. filed May 20, 2014), *available at* www.justice.gov/sites/default/files/osg/briefs/2013/01/01/2012-1351.pet.ami.inv.pdf (emphasis added).

district court erred by holding plaintiff Kathryn Jones's claims preempted, when the FDA's approval of Medtronic's product for a different use imposed no device-specific requirements on the subject of the state-law claims at issue here: namely, the proper design and the necessary warnings when the product is used as it was in this case. This Court should reverse to correct this error and the district court's fundamental misunderstanding of preemption jurisprudence.

BACKGROUND

This case arises from a state-law damages suit brought by Kathryn Jones to recover for severe injuries caused by spinal bone graft products manufactured by respondent Medtronic, Inc. Ms. Jones alleges that her injuries were directly attributable to Medtronic's marketing of the products for use in a way that posed threats of serious injury and that had not been approved by the FDA. Because an understanding of the structure of the MDA is important to understanding this case, Part 1 below offers a general description of the MDA. Part 2 sets forth the facts surrounding Medtronic's promotion of the Infuse device for an unapproved use.

1. Medical Device Regulation

Although prescription drugs have been the subject of extensive regulation by the FDA since the enactment of the Food, Drug, and Cosmetic Act in 1938, medical devices, which range in complexity from bandages to artificial hearts, were outside the scope of the FDA's regulatory authority until the enactment of the MDA in 1976.

See Lohr, 518 U.S. at 475–76. The MDA divided medical devices into three categories—classes I, II, and III—and established a tripartite scheme for their regulation. *See id.*

Under the MDA, class III devices are those that treat serious medical conditions or pose serious risks of causing injury to patients. 21 U.S.C. § 360c(a)(1)(C).[3] Like new drugs, new class III devices that are not substantially similar to devices already on the market when the MDA was enacted must receive premarket approval (PMA) from the FDA. *See Lohr*, 518 U.S. at 477; *Riegel*, 552 U.S. at 318–19. The PMA process involves a detailed review of a device's safety and effectiveness for particular uses, including all studies and investigations available to the manufacturer, as well as the device's proposed uses, design, and labeling. *See Riegel*, 552 U.S. at 318. PMA represents an FDA finding that the device is safe and effective "under the conditions of use included in the proposed labeling." 21 U.S.C. § 360e(d)(1)(A); *see also id.* § 360e(d)(2)(A), (B) (requiring the FDA to deny approval if a device is not safe and effective for the uses recommended or suggested in the labeling).

In addition, PMA is conditioned on the manufacturer's compliance with ongoing obligations under FDA regulations, including the requirement that the

[3] Class I devices are basic items such as bandages and tongue depressors. Class II devices include items, such as hearing aids, that are more complex and have greater potential to cause harm if defective or misused.

manufacturer report adverse incidents involving the device to the FDA. *Id.* § 360i(a)(1), (3); *see Riegel*, 552 U.S. at 319. A manufacturer must report incidents in which a device "malfunctions" and those in which the device may have caused or contributed to a death or "serious injury." 21 C.F.R. § 803.50(a); *see also id.* § 803.3 (defining "malfunction" and "serious injury"). The FDA makes such reports available to the public. *See id.* § 803.9.

In contrast to new class III devices that are subject to the PMA process, class III devices that were already in existence when the MDA was enacted are subject to less stringent standards. Such devices are grandfathered for uses that existed when the statute was passed. Approval to market devices that are "substantially equivalent" to grandfathered devices may be obtained through a truncated review process generally referred to as the "510(k) process" (so named after the MDA section providing for such review). 21 U.S.C. § 360(k); *see Lohr*, 518 U.S. at 477–79. Section 510(k) review focuses on the question of substantial equivalency and does not entail a thorough examination of the device's safety and effectiveness, or of its design, except to the extent necessary to determine whether it is substantially equivalent to a grandfathered device for the same use. *Riegel*, 551 U.S. at 322. To market a grandfathered or substantially equivalent device for a *new* use, however, a manufacturer must obtain PMA. *See* 21 C.F.R. § 807.92(a)(5); FDA, Guidance for Industry: The 510(k) Program: Evaluating Substantial Equivalence in Premarket

Notifications 17 (July 2014), *at* http://www.fda.gov/downloads/MedicalDevices/.../UCM284443.pdf.

Whether a device is introduced through the PMA or 510(k) process, the FDA's approval or clearance is specific to the use(s) specified in the product's labeling. *See* 21 U.S.C. § 360e(d)(1)(A) (in evaluating a PMA application, FDA "shall rely on the conditions of use included in the proposed labeling"); *id.* § 360c(a)(2)(B) (providing that the safety and effectiveness of a device must be determined "with respect to the conditions of use prescribed, recommended, or suggested in the labeling of the device"); FDA, Guidance for Industry: The 510(k) Program, *supra*, at 16-18. Thus, for example, before a manufacturer can market a device approved as a knee implant for use as a hip implant, it must first obtain a supplemental approval or clearance. Although the FDA does not regulate physicians, who may use a device approved for one use for a different use, *see* 21 U.S.C. § 396, a class III device *intended by the manufacturer* for an unapproved, or "off-label," use is adulterated and misbranded. *Id.* §§ 351(f)(1)(B), 352(f).[4] And federal law prohibits manufacturing or marketing an adulterated or misbranded product. *Id.* § 331(a), (b), (c), (g).

[4] *See also* FDA, Guidance for Industry: Good Reprint Practices of the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices (Jan. 2009), *at* www.fda.gov/regulatoryinformation/guidances/ucm125126.htm.

In addition to provisions addressing device classification, approval, and reporting requirements, the MDA contains a provision that preempts any state-law requirement with respect to a medical device that is "different from, or in addition to, any requirement" applicable to the device under the MDA and that "relates to the safety or effectiveness of the device." *Id.* § 360k(a). The FDA has underscored the plain language of the statute by promulgating an implementing regulation that provides that state laws are preempted "only when the [FDA] has established specific counterpart regulations or there are other specific requirements applicable to a particular device under the act," 21 C.F.R. § 808.1(d), and that, even when such specific requirements exist, the MDA "does not preempt State or local requirements that are equal to, or substantially identical to, requirements imposed by or under the act," *id.* § 808.1(d)(2).

2. Medtronic's Infuse Device

The Infuse Bone Graft/L-CAGE Lumbar Tapered Fusion Device (Infuse) consists of a cage and bio-engineered bone-filling material with a carrier or scaffold. Infuse is used in spinal fusion surgery as an alternative to grafting a patient's own bone. The bone-filling material, a protein called rhBMP-2, helps fuse vertebrae in

the lower (lumbar) spine to treat degenerative disc disease. *See* Medtronic, Questions and Answers – Infuse Bone Graft and LT Cage Device. [5]

As a class III medical device, Infuse could not be marketed until Medtronic obtained PMA from the FDA, which it did in 2002. The FDA approved Infuse for use only in surgery in which the surgeon approaches *from the front* (anterior) of the patient, to treat degenerative disc disease in the lower, or lumbar, region of the spine,[6] as the FDA approval letter expressly stated. Infuse is not approved for use in spinal surgery in which the surgeon proceeds through the patient's *back* (posterior). That use creates an undue risk of unwanted bone growth, intractable pain, weakness, and foot drop, among other things.

Nonetheless, Medtronic aggressively promoted Infuse for use in posterior-approach surgeries. As the Department of Justice, a Committee of the United States Senate, and a leading journal of spinal medicine have documented, Medtronic's illegal promotion included paying kickbacks and other incentives to physicians to influence clinical studies, prevent publication of adverse events, and encourage the unapproved use.

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[5] At http://www.medtronic.com/us-en/patients/treatments-therapies/bone-graft-lumbar-degenerative-disc-disease/questions-and-answers.html.

[6] Medtronic later received PMA to market Infuse for use in certain dental surgeries and for repair of certain tibial fractures. Those uses are not pertinent here.

Medtronic was a defendant in two qui tam lawsuits alleging that it violated the False Claims Act, 31 U.S.C. § 3729, by paying illegal kickbacks to physicians for promoting the off-label use of Infuse, which resulted in the submission of false or fraudulent claims to federal health care programs. In July 2006, Medtronic agreed to pay $40 million to settle these lawsuits. *See* Armstrong & Burton, *Medtronic linked to surgery problems*, Wall St. J., Sept. 4, 2008.

Despite the settlement, Medtronic continued to market Infuse for the unapproved use in posterior-approach spinal surgery. In 2008, a Wall Street Journal article about Medtronic's practices reported on problems with off-label use of Medtronic's Infuse, including that Medtronic gave payments to physicians, in the form of consulting agreements, as a means of increasing sales of Infuse. *Id*.

In June 2011, the Senate Committee on Finance began an investigation into whether Medtronic was continuing to misrepresent the adverse events that resulted from Infuse, as well as the possibility that Medtronic used payments to physicians to improperly influence clinical trials and reporting. *See* U.S. Sen., Committee on Finance, *Staff Report on Medtronic's Influence on Infuse Clinical Studies* at 1 (Oct. 25, 2012).[7]

[7] *Available at* https://www.finance.senate.gov/imo/media/doc/Medtronic_Report3.pdf.

The next week, *The Spine Journal*, a leading U.S. medical journal, published a special edition dedicated to addressing serious patient safety and ethical concerns related to the use of Infuse in the spine. The journal reviewed thirteen peer-reviewed articles about rhBMP-2 by industry-sponsored authors, including many sponsored by Medtronic, and found that these articles had inaccurately reported the device's safety by underestimating the risks. In an editorial summarizing the journal's findings, five prominent physicians, including spine surgeons at Stanford University, wrote that the earlier industry-sponsored trials and reports were "remarkable for the complete absence of reported rhBMP-2–related clinical adverse events," including reported instances of adverse back and leg pain events, radiculitis, bone resorption, urinary retention, and implant displacement, as well as sterility and cancer risks. Eugene J. Carragee, et al., *A challenge to integrity in spine publications: years of living dangerously with the promotion of bone growth factors*, 11 The Spine Journal 463 (June 2011).[8] They concluded that the trials and reports suffered from idiosyncratic trial design, reporting bias, and peer-review and publication shortfalls. *Id*. According to the editorial and accompanying articles, the thirteen industry-sponsored articles reported only successful fusions and low rates of complications with Infuse, "which led to the 'off-label' use of Infuse" and "may

[8] *Available at* http://www.researchgate.net/publication/51467883_A_challenge_to_integrity_in_spine_publication_Years_of_living_with_the_promotion_of_bone_growth_factors.

have promoted widespread poorly considered on- and off-label use, eventual life-threatening complications and deaths." *Id*.

In 2012, the Senate Finance Committee Chairman released the results of its 16-month investigation into Medtronic. *See* U.S. Sen., Committee On Finance, *Baucus-Grassley Investigation into Medtronic Reveals Manipulated Studies, Close Financial Ties with Researchers* (Oct. 25, 2012).[9] The investigation revealed that, "[w]ithout public disclosure of their roles, Medtronic employees collaborated with physician authors to edit—and in some cases, write—segments of published studies on its bone-growth product InFuse," which "may have inaccurately represented InFuse's risks and may have placed added weight on side effects of alternative treatments." *Id*. The investigation also found that Medtronic "maintained significant, previously-undisclosed financial ties with physicians who authored studies about InFuse, making $210 million in payments to physicians over a 15-year period." *Id*.

In 2016, A Minneapolis *Star Tribune* investigation revealed that, in a Medtronic study of Infuse shut down in 2008, the company had received more than 1,000 adverse events reports from physicians. *See* Jim Spencer, et al., *Question of*

[9] *At* https://www.finance.senate.gov/chairmans-news/baucus-grassley-investigation-into-medtronic-reveals-manipulated-studies-close-financial-ties-with-researchers.

Risk, Medtronic's Lost Study, Star Tribune, Apr. 10, 2016.[10] Although federal regulations required that the reports be submitted to the FDA within 30 days of receipt by Medtronic, the company failed to report the vast majority for more than five years. *Id*.

Meanwhile, in 2010, Kathryn Jones had three back surgeries involving unapproved uses of Infuse. For purposes of this appeal, it is undisputed that Medtronic's off-label promotion caused the products to be used in ways not evaluated by the FDA for safety and effectiveness and not approved by the FDA for use in patients.

SUMMARY OF ARGUMENT

The district court's preemption analysis reflects a fundamental misreading of the scope of both express preemption under § 360k(a) of the MDA and implied preemption. Express preemption was the primary basis for the court's dismissal of Ms. Jones's claims, and accordingly this brief will focus on that issue.

Section 360k(a) by its plain terms preempts only state laws that impose requirements that are "different from, or in addition to," requirements under the MDA. As the U.S. Supreme Court's decision in *Medtronic, Inc. v. Lohr* makes clear, if no relevant federal requirements are in place, state law is not preempted. The FDA

[10] *Available at* http://www.startribune.com/question-of-risk-medtronic-s-lost-infuse-study/372957441/.

does not approve medical devices in some general sense; it approves them for specific uses and imposes requirements applicable to those uses. Here, Ms. Jones's alleges—and for purposes of the motion to dismiss those allegations are taken as true—that Medtronic marketed Infuse for uses never approved by the FDA, such as for use in posterior-approach surgery. By definition, the FDA imposes no requirements on the design, labeling, or promotion of products for *unapproved* uses. As in *Lohr*, in the absence of federal requirements, § 360k(a) does not preempt Ms. Jones's state-law claims. *See Lohr*, 518 U.S. at 493 (no preemption where FDA marketing clearance did not involve a determination of safety and effectiveness).

ARGUMENT

Section 360k(a) preempts state-law requirements only when they are "different from, or in addition to," federal medical device requirements. The duties underlying Ms. Jones's state-law claims do not fall within the scope of § 360k(a). Medtronic's Infuse device was subject to no federal requirements regarding uses that the FDA did not approve. Ms. Jones's claims are therefore not preempted to the extent that they stem from injuries caused by Medtronic's off-label promotion of Infuse.[11]

[11] In addition, as this Court held in its en banc decision in *Stengel*, 704 F.3d 1224, § 360k(a) does not preempt state-law requirements that parallel federal device requirements. *See Lohr*, 518 U.S. at 495–97; *Riegel*, 522 U.S. at 330. Thus, Ms. Jones's claims are also not preempted for the additional reason that they are based on state-law duties that impose liability for conduct that also violates federal

I. In the absence of an applicable federal requirement, § 360k(a) does not preempt state law.

By its express terms, the MDA's preemption provision, § 360k(a), preempts only state laws that impose requirements with respect to devices that are "different from, or in addition to," requirements applicable to the same devices under the MDA. The FDA has underscored the plain language of the statute by promulgating a regulation implementing it, which provides that state laws are preempted "only when the Food and Drug Administration has established specific counterpart regulations or there are other specific requirements applicable to a particular device under the act," 21 C.F.R. § 808.1(d), and that even when such specific requirements exist, the MDA "does not preempt State or local requirements that are equal to, or substantially identical to, requirements imposed by or under the act," *id.* § 808.1(d)(2).

Reiterating this same point, the Supreme Court in both *Lohr* and *Riegel* held that the touchstone for preemption under § 360k(a) is the existence of requirements specifically applicable to a device, which preempt state requirements that impose different or additional requirements with respect to the subject-matter covered by the federal requirements. *See Riegel*, 552 U.S. at 322–23; *Lohr*, 518 U.S. at 493–94,

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requirements. Ms. Jones's supplemental brief (at III) explains why that case law supports her here, and this amicus brief will not address that point further.

498–502. In *Lohr*, the Court considered state-law design, labeling, and manufacturing claims concerning a Medtronic device marketed through the FDA's 510(k) process. As relevant here, the Court unanimously held that § 360k(a) did not preempt the Lohrs' design claim, stating that state law is not preempted if no relevant federal requirement is in place. 518 U.S. at 492-94 (majority opinion) (design defect claim not preempted where federal law places no design requirements on the device); *id*. at 513 (O'Connor, J., concurring in part) (same). The Court emphasized that preemption under § 360k(a) turns on the existence of *specific* federal and state requirements on the same subject matter and noted that "it is impossible to ignore [the statute's] overarching concern that pre-emption occur only where a particular state requirement threatens to interfere with a specific federal interest." 518 U.S. at 500; *id.* at 492–94 (state-law design defect claims not preempted because 510(k) clearance process did not result in imposition by the FDA of specific requirements applicable to device design).

In *Riegel*, the Supreme Court considered the scope of § 360k(a) in a case that, like this one, involved a class III Medtronic device marketed under a PMA, rather than the abbreviated 510(k) review at issue in *Lohr*. Again applying two-step approach to determining whether state-law claims are preempted, the Court agan explained that preemption under § 360k(a) requires specific federal requirements applicable to the device, which then operate to preempt different or additional state-

law requirements addressing the same subjects. *See* 552 U.S. at 322–23. Thus, the Court held that state-law design defect and failure-to-warn claims are preempted *to the extent* that they would impose requirements different from or in addition to the specific design and labeling requirements imposed by federal law on PMA devices and address the same subject-matter as those requirements. *See id.* at 325. The Court's analysis in *Riegel* rests heavily on the notion that the adequacy of the design and labeling of devices for approved uses are matters specifically reviewed and approved by the FDA in the PMA process. *Id*. at 318, 323.

Together, the Supreme Court's decisions in *Lohr* and *Riegel* establish unequivocally that § 360k(a) does not preempt state-law claims in the absence of a relevant federal device requirement. Such state-law duties, by definition, do not contain specific requirements that are "different from, or in addition to," federal requirements.

Thus, when a manufacturer markets a device for an unapproved use, § 360k(a) plays no role. In such circumstances, the manufacturer acts outside the scope of the FDA's device-specific design and labeling requirements, because, as to that use, the FDA has not reviewed and approved the safety and effectiveness of the device and the adequacy of the warnings and instructions for use contained in its labeling. The MDA specifically provides that, for purposes of PMA, the FDA evaluates only the particular uses described in the manufacturer's proposed labeling

for the device: "[T]he safety and effectiveness of a device are to be determined—(A) with respect to the persons for whose *use the device is represented or intended*; (B) with respect to the *conditions of use* prescribed, recommended, or suggested in the labeling of the device; and (C) weighing any probable benefit to health from the *use of the device* against any probable risk of injury or illness *from such use*." 21 U.S.C. § 360c(a)(2) (emphasis added). The FDA's decision to grant or withhold PMA depends on whether it finds a reasonable assurance of safety and effectiveness "*under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof*," *id.* § 360e(d)(2) (emphasis added), and approval authorizes the manufacturer to market the device only for that use.

II. Because the FDA has imposed no requirements on posterior-approach use of infuse, claims arising from marketing and promotion for that off-label use are not preempted.

This case involves claims based on specific uses of the Infuse device: its use for posterior spinal fusion surgery and along both sides of the spine, at seven levels. *See* SER 688–670 (Complaint). The FDA has never approved the device for those uses and hence has never imposed requirements on the design and labeling of the device for those uses.

Here, while PMA for the Infuse device imposes specific design and labeling requirements that Medtronic must meet when marketing Infuse for its *approved* use in anterior spinal surgery, the PMA imposes *no* design or labeling requirements on

Infuse as a device *intended by Medtronic* for use in posterior spinal surgery or at other levels of the spine. The FDA's PMA for *other* uses of Infuse does not require that a device intended for use in posterior spinal surgery "take any particular form for any particular reason," *Lohr*, 518 U.S. at 493, nor does the PMA specify labeling requirements for a device marketed for that use. When it granted PMA, the FDA neither considered nor approved the safety and effectiveness of Infuse's design for posterior surgery or the adequacy of the device's labeling for that use. The PMA decision thus established no requirements applicable to the Infuse device intended by Medtronic for posterior-approach spinal fusion. Under the reasoning of *Lohr* and *Riegel*, therefore, there are no specifically applicable federal requirements that preempt state requirements applicable to the design or labeling of the device to the extent it is intended for use in, and marketed for use in, posterior spinal surgery.

Thus, Medtronic's observation (Appellee Br. 7 n.1 (filed Dec. 14, 2015) (hereafter "2015 Appellee Br.")) that the use to which the doctor put the device in *Riegel* was unapproved is irrelevant. The plaintiffs in *Riegel* did not allege that the manufacturer had marketed the device for an unapproved use. *See Riegel*, 552 U.S. at 320 (describing facts). The Supreme Court decided the case on the premise that the manufacturer had complied with the terms of the PMA, which imposed design and labeling requirements applicable to the device when marketed for the approved uses. *See id.* at 339. In those circumstances, *Riegel* held, state-law claims based on

a duty to design and label the device differently from the federal requirements would impose different or additional requirements on the manufacturer. *See id*. at 323–34. To be sure, the Infuse device's PMA provides design and labeling requirements that are "applicable to the device" *when it is manufactured and marketed for the uses specified in its labeling*. But the PMA does not impose design or labeling requirements that are "applicable" to Infuse when Medtronic markets the device for an unapproved use. Absent any such *applicable* requirement, the fact that the device may be subject to other *inapplicable* requirements is irrelevant.

The district court's contrary conclusion would distort the evident purposes of § 360k(a) as described in both *Lohr* and *Riegel*: protecting the FDA's determinations of a device's safety and effectiveness, incorporated in specific requirements imposed in the PMA process, from second-guessing by state laws. *See Riegel*, 552 U.S. at 325; *Lohr*, 518 U.S. at 500. When a manufacturer markets a device for an unapproved use, no such FDA determinations are implicated because the FDA has not assessed the safety and effectiveness of the device for that use and has not imposed federal design and labeling requirements to ensure the adequacy of the device for that use. Extending preemption under § 360k(a) to claims against manufacturers who market devices for unapproved uses would grant them a windfall: protection from state-law liability for engaging in conduct that is not only unauthorized by federal law, but actually prohibited.

III. Debate over FDA restrictions on "off-label" promotion is not pertinent here.

In its 2015 Appellee Brief (at 6), Medtronic emphasized that doctors can prescribe a device for uses not approved by the FDA. Physicians' ability to prescribe, however, does not alter the fact that the FDA has, by definition, not approved the product for off-label uses. Rather, it reflects that the FDA does not regulate the practice of medicine. *See*, *e.g.*, FDA, Guidance for Industry—Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices 2 (2011) (FDA 2011 Guidance).[12] Importantly, that the FDA imposes no requirements on doctors does not speak to the nature of the requirements it imposes on device manufacturers. The FDA approves the marketing of devices under the "conditions of use included in the proposed labeling" submitted with the PMA application. 21 U.S.C. § 360e(d)(1), (2); *see id.* § 360c(a)(2); *see generally Riegel*, 552 U.S. at 317–19. A PMA device marketed for the uses specified in its labeling is subject to the design and labeling requirements imposed by the FDA upon approval, and under § 360k(a), a manufacturer that markets the device for its approved use may not be subjected to state requirements that differ from or add to those requirements. *See Riegel*, 552 U.S. at 323–25.

[12] *At* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM285145.pdf.

By contrast, because the FDA "rel[ies] on the conditions of use included in the proposed labeling as the basis for determining whether or not there is a reasonable assurance of safety and effectiveness," 21 U.S.C. § 360e(d)(1), PMA does not represent a finding that the device is safe and effective apart from the approved use(s). And PMA does not impose requirements on how a manufacturer can design and label a device for a use not specified in the proposed labeling (uses that necessarily have not been found safe and effective by the FDA). Rather, "requirements applicable to the device" are "premised on the manufacturer's intended use," and when a manufacturer markets a device for an off-label use, "it [has] departed the realm of federal regulation and returned to the area of traditional state law remedies." *Ramirez v. Medtronic, Inc.*, 961 F. Supp. 2d 977, 991, 993 (D. Ariz. 2013). "In the absence of federal approval of the new use, there is nothing to preempt state law requirements." *Id*. at 993.

Thus, a PMA device marketed by its manufacturer for approved uses is indisputably subject to applicable federal design and labeling requirements, and a physician's decision to use the device for an off-label purpose for which the manufacturer has not promoted it does not alter the preemptive effect of § 360k(a). As explained in *Ramirez*, when the manufacturer confines itself to marketing the device for approved uses and complies with the requirements applicable to the device when marketed for those uses, a claim that the manufacturer "should have

provided additional warnings or designed the product differently in light of [an] unapproved use … is asking the manufacturer to do something 'different from, or in addition to' federal law." *Ramirez*, 2013 WL 4446913, at *8. In such cases, "[t]he doctor's off-label use is not a result of the manufacturer's conduct; indeed, the manufacturer in this situation is adhering to federal law." *Id*.

Medtronic errs in relying on *Perez v. Nidek Co.*, 711 F.3d 1109 (9th Cir. 2013), which does not address the consequences of a manufacturer's marketing its device for an unapproved use. *Perez* holds that § 360k(a) preempts state-law fraud claims premised on the theory that a manufacturer should have provided warnings in addition to those required by the PMA, because the manufacturer "knew or should have known" that doctors were using the device for unapproved indications without telling their patients that the uses were not FDA approved. *Id*. at 1117.[13] A manufacturer that markets its product only for approved uses, the court held, cannot be held liable for failure to take steps not required by the FDA to warn against unapproved uses. *See id.* at 1118–19. Thus, "[t]here is a crucial difference between a claim premised on a physician's use of a device that is unsanctioned by both the FDA and the manufacturer, and one based on a use that still lacks FDA scrutiny but is actively promoted by the manufacturer." *Ramirez*, 2013 WL 4446913, at *11.

[13] *Perez* recognized that the device was subject to the requirement that the manufacturer not "introduce[] [it] into commerce" for unapproved uses. *Perez*, 711 F.3d at 1118.

Moreover, Medtronic's reliance (2015 Appellee Br. 22–23) on the decision in *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2010), is a red herring. *Caronia* held that a criminal prosecution based only on promotional speech violated the First Amendment. *See id.* at 152. It also recognized that when a manufacturer *intends* a drug or device for an off-label use, the product is misbranded because its label does not contain adequate directions for that use. *See id.* at 154, 160–62. *Caronia* thus does not hold that federal law permits (let alone authorizes) a manufacturer to market a device for unapproved uses. In any event, nothing in *Caronia* questions the fact that, by definition, an off-label use is one that the FDA has not evaluated and approved as safe and effective. *Caronia* thus does not speak to the preemption question: whether, with respect to unapproved uses, a medical device falls into the category of devices at issue in *Lohr*, not *Riegel*. *See Lohr*, 518 U.S. at 493–94 (no preemption where no FDA determination of safety and effectiveness), and *Riegel*, 552 U.S. at 322-23 (preemption where device marketed pursuant to PMA). Because FDA approval of the device for the uses specified in its labeling does not impose requirements applicable to the device *as marketed for other uses*, there is no preemption here.

Although Medtronic questioned the fact in its initial brief (at 22), the FDA has repeatedly made clear that PMA, far from imposing requirements as to how a device marketed for an *unapproved* use must be designed and labeled, forbids off-label

marketing by device manufacturers. As the FDA has explained, "the [FDCA] and FDA's implementing regulations generally prohibit manufacturers of new drugs or medical devices from distributing products in interstate commerce for any intended use that FDA has not approved as safe and effective," and "a medical device that is promoted for a use that has not been approved or cleared by FDA is adulterated and misbranded." FDA, Guidance for Industry—Good Reprint Practices, *supra*, n.4.

* * * *

In sum, under *Riegel*, preemption is triggered by FDA evaluation and approval for the conditions of use stated in the labeling. The FDA did not evaluate and approve the Infuse products for the uses for which Medtronic promoted them, leading to Ms. Jones's injury. Medtronic cannot reasonably rely on "the existence of federal regulations it is allegedly circumventing to justify" preemption. *Ramirez*, 2013 WL 4446913, at *10.

CONCLUSION

For the foregoing reasons, the decision of the district court should be reversed.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that I electronically filed the foregoing with the Clerk of the Court for the United States Court of Appeals for the Ninth Circuit by using the appellate CM/ECF system on December 18, 2017. I certify that all participants in the case are registered CM/ECF users and that service will be accomplished by the appellate CM/ECF system.

/s/ .
Allison M. Zieve

CERTIFICATE OF COMPLIANCE

The brief's type size and type face comply with Fed. R. App. P. 32(a)(5)and (6). This brief is 5,550 words, excluding the portions exempted by Fed. R. App. P. 32(a)(7)(B)(iii), if applicable.

/s/ .
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