NO. _____

In the
Supreme Court of the United States

WILLIAM FACTEAU AND PATRICK FABIAN,

Petitioners,

v.

UNITED STATES OF AMERICA,

Respondent.

On Petition for Writ of Certiorari to the United States Court of Appeals for the First Circuit

PETITION FOR WRIT OF CERTIORARI

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March 13, 2024

QUESTIONS PRESENTED

Petitioners were convicted of introducing into interstate commerce a "misbranded" and "adulterated" medical device. 21 U.S.C. § 331(a). That provision prohibits the distribution of an FDA-cleared device if the manufacturer has an off-label "intended use" for the device—*i.e.*, a use different from the one cleared by FDA. FDA regulations provide that "intended use" is determined by the manufacturer's "objective intent," which may be shown by (i) a manufacturer's "expressions," such as "advertising matter" or other "oral or written statements"; and (ii) the circumstances surrounding the distribution of the article," including "circumstances in which the article is, with the knowledge of [the manufacturer], offered and used for a purpose for which it is neither labeled nor advertised." 21 C.F.R. §§ 201.128, 801.4 (2016 ed.). Because off-label uses are lawful and ubiquitous, such "circumstances" are ubiquitous as well. The "intended use" regulations thus effectively criminalize both truthful, non-misleading speech about off-label uses and "knowledge" of common and lawful "circumstances."

The questions presented are:

1. Whether FDA's "intended use" regulations violate the First Amendment by requiring manufacturers to refrain from truthful, non-misleading speech about off-label uses.

2. Whether FDA's "intended use" regulations violate the Fifth Amendment by encouraging arbitrary enforcement and denying fair notice of what conduct may lead to prosecution.

RELATED PROCEEDINGS

This case arises from the following proceedings:

- *United States v. Facteau*, 89 F.4th 1 (1st Cir. 2023).
- *United States v. Facteau*, No. 15-cr-10076, 2020 WL 5517573 (D. Mass. Sept. 14, 2020). Judgment entered Jan. 20, 2021.
- *United States v. Facteau*, No. 15-cr-10076 (D. Mass. July 20, 2016), ECF No. 432.

There are no other proceedings in state or federal trial or appellate courts, or in this Court, directly related to this case under Rule 14.1(b)(iii).

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PETITION FOR WRIT OF CERTIORARI

Petitioners William Facteau and Patrick Fabian respectfully petition for a writ of certiorari to review the judgment of the First Circuit.

OPINIONS BELOW

The First Circuit's opinion (App.1) is reported at 89 F.4th 1. The district court's opinion denying Petitioners' post-trial motions (App.93) is available at 2020 WL 5517573.

JURISDICTION

The First Circuit issued its opinion on December 14, 2023. This Court has jurisdiction under 28 U.S.C. § 1254.

PROVISIONS INVOLVED

Relevant constitutional, statutory, and regulatory provisions are reproduced in the Appendix. App.170.

STATEMENT

A. Off-label use of drugs and devices

Before a manufacturer of drugs or medical devices may introduce a product into interstate commerce, the manufacturer must first seek FDA approval. New drugs and class III devices must receive "premarket approval." 21 U.S.C. §§ 355, 360e. Devices that are "substantially equivalent" to a "predicate device" already on the market may instead receive "510(k) clearance." App.4; *see* 21 U.S.C. § 360c(f). FDA's finding of substantial equivalence means that, among other things, a device is as safe and effective as the predicate device. 21 C.F.R. § 807.100(b)(2)(ii)(B). When FDA approves or clears a product, it also

approves a label that lists the uses for which the product was approved or cleared. 21 U.S.C. §§ 355(b)(1)(A), 355(d), 360e(c)(1)(F), 360e(d).

Once a product has been approved or cleared, it is perfectly legal for doctors to use or prescribe it for uses that do not appear on the FDA-approved label. Such "off-label" use "is an accepted and necessary" medical practice. *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 (2001); *see Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 196, 201–02 (S.D.N.Y. 2015). FDA has long acknowledged that "the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgment." FDA, Information Sheet: "Off-Label" and Investigational Use of Marketed Drugs, Biologics, and Medical Devices (Jan. 1998), https://tinyurl.com/yub6h9bx.

Many medical products are commonly or even principally used off-label. Indeed, off-label use is often the standard of care—meaning doctors may be liable for malpractice if they stick to FDA-approved uses. *See* John E. Osborn, *Can I Tell You the Truth? A Comparative Perspective on Regulating Off-Label Scientific and Medical Information*, 10 Yale J. Health Pol'y, L. & Ethics 299, 304 (2010). One study found that approximately 21% of drug prescriptions were for off-label uses. Randall S. Stafford, *Regulating Off-Label Drug Use—Rethinking the Role of the FDA*, 358 New Engl. J. Med. 1427, 1427 (2008). Aspirin, for example, was widely prescribed off-label to reduce the risk of heart attack before FDA approved that use. Off-label use is common in oncology, where doctors and patients cannot afford to wait many years before a

drug is approved for a specific cancer.[1] Almost all devices in pediatric surgery are used off-label, a practice the American Academy of Pediatrics has called "necessary."[2] And off-label uses are rampant in otolaryngology, the field at issue in this case. *E.g.*, CA1 JA1187–93, 1527–35, 1805–07, 1965–69.

Underscoring the value of off-label use, Congress prohibited FDA from "limit[ing] or interfer[ing] with the authority of a health care practitioner to prescribe or administer any legally marketed device." 21 U.S.C. § 396. That ensures doctors "have the flexibility to draw on their expertise to prescribe or administer the device for any condition or disease, not just the use the FDA approved." *Judge Rotenberg Educ. Ctr., Inc. v. FDA*, 3 F.4th 390, 395 (D.C. Cir. 2021); *accord Caplinger v. Medtronic, Inc.*, 784 F.3d 1335, 1344 (10th Cir. 2015) (Gorsuch, J.). Congress also requires Medicaid and Medicare to reimburse treatments that are "medically accepted"—even if off-label. 42 U.S.C. §§ 1396r-8(d)(1)(B)(i), 1395y(a)(1)(A).

B. Criminalization of off-label promotion

1. Consistent with Congress's approval of off-label use, the FDCA "do[es] not expressly prohibit the 'promotion' or 'marketing' of drugs [or devices] for off-label use." *United States v. Caronia*, 703 F.3d 149,

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[1] Am. Cancer Soc'y, *Off-Label Drug Use* (2021), https://tinyurl.com/544bsvak.

[2] Am. Acad. of Pediatrics, *Off-Label Use of Medical Devices in Children* 139 Pediatrics 1, 1 (2017), https://tinyurl.com/u4vzzh8s; *see also Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 56 (D.D.C. 1998), *vacated in part sub nom. Wash. Legal Found. v. Henney*, 202 F.3d 331 (D.C. Cir. 2000).

154–55 (2d Cir. 2012). Instead, "the Government continues to prosecute th[at] conduct by patching together" FDCA provisions prohibiting "adulterated" and "misbranded" drugs and devices. App.94; 21 U.S.C. §§ 331, 351, 352.

A device is "adulterated" and "misbranded" if the manufacturer has an off-label "intended use" for it. A product is "misbranded" if its label does not bear "adequate directions for use," *id.* § 352(f)(1), which FDA defines as directions under which the product can be used "safely and for the purposes for which it is intended." 21 C.F.R. §§ 201.100(c)(1), 201.5, 801.109(d), 801.5. In addition, devices are "misbranded" and "adulterated" if the manufacturer has an intended use for which it did not obtain premarket approval or clearance. 21 U.S.C. §§ 351(f), 360c(i), 360e(c)(2)(A)(iv).

As relevant here, Congress did not define or even use the term "intended use"; it is a creature of FDA regulations, which say it "refer[s] to the objective intent" of the manufacturer. 21 C.F.R. §§ 201.128, 801.4. These regulations provide that "objective intent" can be determined by a manufacturer's "expressions," such as "labeling claims, advertising matter, or oral or written statements." *Id.* But they also provide that "objective intent" can be determined by all "circumstances surrounding the distribution of the article," including "circumstances in which the article is, with the knowledge of [the manufacturer], offered or used for a purpose for which it is neither labeled nor advertised." *Id.* By making the lawfulness of distributing an approved product depend on whether the manufacturer has an off-label "intended

use"—which FDA defined extremely broadly based on the novel concept of "objective intent"—FDA created a sweeping criminal prohibition that did not exist in the FDCA.

FDA's "intended use" regulations have been amended a few times since their adoption, but their substance has never meaningfully changed. The first regulation, adopted in 1952—before this Court recognized First Amendment protection for commercial speech—provided that "intended use[]" refers to "objective intent," which "is determined by [the manufacturer's] expressions or may be shown by the circumstances surrounding the distribution of the article," including if "the article is, with the knowledge of [the manufacturer] or [its] representatives, offered and used for a purpose for which it is neither labeled nor advertised." 17 Fed. Reg. 6818, 6820 (July 25, 1952). "[N]onsubstantive" amendments in 1975 and 1976 recodified the 1952 regulation separately for drugs and devices. 40 Fed. Reg. 13,996, 13,996, 14,007 (Mar. 27, 1975); 41 Fed. Reg. 6896, 6896–97 (Feb. 9, 1976).

The current version of the regulations became effective in September 2021, after the trial in this case. 86 Fed. Reg. 41,383 (Aug. 2, 2021).[3] They are substantively identical to the 1952 regulation, with one qualification: "[A] firm would not be regarded as intending an unapproved new use for a" product "based *solely* on that firm's knowledge that [it] was

[3] In January 2017, FDA announced "clarifying changes" that did not alter the regulations' meaning or "reflect a change in FDA's approach regarding evidence of intended use," 82 Fed. Reg. 2193, 2204 (Jan. 9, 2017), but FDA indefinitely delayed those amendments in March 2018, 83 Fed. Reg. 11,639 (Mar. 16, 2018).

being prescribed or used by health care providers for [an off-label] use." 21 C.F.R. §§ 201.128, 801.4 (emphasis added). FDA said these amendments "clarifie[d] but d[id] not change FDA's interpretation and application of existing intended use regulations for medical products." 86 Fed. Reg. at 41,399.[4]

2. As written, the intended-use regulations permit FDA to find a new "intended use"—thus criminalizing the sale of an approved product—based on any "circumstance[] surrounding [its] distribution." 21 C.F.R. §§ 201.128, 801.4. Given the ubiquity of off-label use and the reality that manufacturers know how their products are used, taking this language seriously would mean that most manufacturers are committing a crime by distributing their FDA-approved products, because most manufacturers know their products are used off-label. The language also criminalizes the distribution of a product if the manufacturer provides a doctor with truthful information about an off-label use, no matter how widely accepted or beneficial.

Recognizing that its regulations' language sweeps so broadly as to seemingly criminalize most medical-product sales and raise serious First Amendment problems, FDA has asked manufacturers to trust it to

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[4] The 2021 amendment also changed the phrase "offered *and* used" to "offered *or* used," but FDA did not intend that to be a substantive change. FDA stated that "offered or used" appeared in the 1952 regulation, 86 Fed. Reg. at 41,386, which is incorrect: until 2021, the regulations read "offered and used." 17 Fed. Reg. at 6820. FDA's error shows it does not believe there is any legal difference between "offered and used" in the earlier regulations and "offered or used" in the current regulations.

exercise its enforcement discretion responsibly. It has issued guidances discussing some "circumstances" covered by the essentially unlimited language of its regulations that, in practice, it generally will or will not treat as creating a new intended use.

FDA's guidances focus on the content of the manufacturer's speech. For example, FDA has said that if manufacturers do not engage in off-label "promotion," they generally will not be prosecuted for having an off-label intended use. *E.g.*, JA517. But no statute or regulation defines "promotion." Similarly, FDA has said manufacturers may engage in "scientific exchange" about off-label uses. *E.g.*, JA234–54. But no statute or regulation defines "scientific exchange" either.

Most recently, FDA proposed guidance on the communication of "scientific information on unapproved uses … of approved/cleared medical products." FDA, Draft Guidance for Industry: Communications from Firms to Health Care Providers Regarding Scientific Information on Unapproved Uses of Approved/Cleared Medical Products Questions and Answers at 1 (Oct. 2023) (cleaned up). The guidance provides that such communications should be "clinically relevant," meaning "pertinent to [doctors] engaged in making clinical practice decisions for the care of an individual patient." *Id.* at 10. But the guidance does not define clinical relevance by reference to what *doctors* believe is relevant. Instead, FDA has decided for *itself* what is relevant to doctors' treatment decisions—and has categorically determined that scientific information about phase II clinical studies does not qualify. *Id.* at 10–12.

Commenters have warned FDA that this approach will "have a stifling impact on dissemination of much groundbreaking research,"[5] "discourage the development and advancement of medical technology,"[6] and "plac[e] [manufacturers] at risk of potentially arbitrary enforcement."[7]

All of these guidances are expressly nonbinding (and some are merely in "draft" form), leaving the sweeping legal rule intact. *See, e.g.,* JA238; 21 C.F.R. § 10.115(d)(1).

C. Petitioners' prosecution and trial

1. Facteau was CEO of a medical-device company called Acclarent, Inc., and Fabian was Vice-President of Sales. App.8–9. This case involves a device called the Stratus Microflow Spacer. App.3.

Initially, beginning in 2005, Acclarent hoped to develop a spacer device that could treat sinusitis by stenting tissue apart while delivering steroids to the sinuses. App.9. As designed, the Stratus could deliver both saline and a steroid called Kenalog. App.106. The use of Kenalog and other steroids to treat sinus conditions is off-label but is nonetheless considered the standard of care by otolaryngologists. *See* JA1191–92, 1528–30, 1803–04, 1967–69.

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[5] AdvaMed, Comment Letter on FDA Draft Guidance on Good Reprint Practices at 4 (Apr. 21, 2008).

[6] Med. Device Mfrs. Ass'n, Comment Letter on FDA Draft Guidance on Good Reprint Practices ("MDMA Comment") at 4 (Apr. 21, 2008).

[7] PhRMA, Comment Letter on FDA Draft Guidance on Good Reprint Practices at 7 (Jan. 5, 2024).

Acclarent's strategy was to first receive 510(k) clearance for use of the device with saline and then later receive an expanded clearance for delivery of steroids. App.10. This kind of "iterative" approach to seeking clearance is common in the medical-device industry. *E.g.*, JA1872–76, 3327–28. Nothing in any statute or regulation requires "manufacturers to list all applicable or intended indications when they first apply for FDA approval." *Caronia*, 703 F.3d at 168; *see Ass'n of Am. Physicians & Surgeons, Inc. v. FDA*, 226 F. Supp. 2d 204, 217–18 (D.D.C. 2002) (FDA "may only regulate claimed uses of drugs, not all foreseeable or actual uses").

In September 2006, FDA cleared the Stratus for use as a spacer. App.10–11. In 2007 Acclarent requested additional clearance for steroid delivery. App.11. FDA denied that request. App.12. In further discussions with FDA through late 2010, Acclarent continued to tell FDA it was seeking clearance for steroid delivery. App.107–08. Acclarent also told FDA that "the majority of physicians" who used the Stratus did so off-label with steroids. App.108. Each of those uses also involved using the Stratus *on*-label as a spacer. Every otolaryngologist who testified at trial agreed that the off-label use of steroids to treat sinus conditions is common, safe, and effective. *See* JA1187–93, 1517, 1528–35, 1797–98, 1803–04, 1912–13, 1965–69. Doctors ordered and re-ordered the Stratus because it was a safe and effective improvement on earlier devices. *See* JA1187–89, 1193, 1338–39, 1535, 1803, 1912, 1919A–19C, 1968, 2036, 2214–15, 2243–44, 3715–17.

Despite knowing that physicians commonly used the Stratus off-label with steroids—and despite knowing that *Acclarent* knew that—FDA took no enforcement action between 2006 and 2015. Over five years, FDA approved five 510(k) clearances for the Stratus, consistent with the accepted practice of incrementally expanding a device's uses through successive clearances. *See* JA1872–76, 3327–28, 4695, 4781, 4797, 5151. Each time, FDA's clearance meant that the new iteration of the Stratus did not raise new questions of safety and effectiveness.

2. In 2015, the government charged Petitioners with one count of conspiracy to commit securities fraud, adulteration, and misbranding; three counts of securities fraud; four counts of wire fraud and attempted wire fraud; five counts of distributing an adulterated device; and five counts of introducing a misbranded device into interstate commerce. App.94–95. Each adulteration and misbranding count was charged as both a felony and a misdemeanor. App.95–96. Misdemeanor adulteration and misbranding are strict-liability crimes, while felony adulteration and misbranding require proof of "intent to defraud or mislead." 21 U.S.C. § 333(a)(1)–(2). The government dropped the securities-fraud charges before trial. App.95.

The trial took twenty-seven days. To prove Petitioners' "objective intent," the government introduced evidence that the Stratus's design allowed both on-label and off-label uses and that Acclarent had studied the possibility of using the Stratus with steroids. *See* App.104–08. The government claimed that evidence proved Acclarent hoped the Stratus

would be used with steroids and intended to seek FDA clearance for that use—which Acclarent disclosed to FDA and would be true of any manufacturer taking an iterative approach to clearance. *See* App.108. The government also introduced evidence that Acclarent knew doctors were using the Stratus off-label—which Acclarent also disclosed to FDA, and which is true of every manufacturer of every product that has off-label uses. *See* App.108.

Finally, the government introduced evidence of Acclarent's speech to healthcare providers, which truthfully disclosed the feasibility of using the Stratus safely to administer steroids. *See* App.109–23. Although the government argued that Acclarent's speech was false and misleading, the jury squarely rejected that theory by acquitting Petitioners of every crime involving fraud or deceit. App.20, 100. The jury convicted Petitioners solely of strict-liability misdemeanor adulteration and misbranding offenses. App.20, 95–96.

D. Post-trial proceedings and appeal

Petitioners moved for judgment of acquittal or a new trial under the First and Fifth Amendments. App.20. Four years later, the district court denied Petitioners' motions. App.21. As that delay "evidenced," the district court "f[ound] the issues raised in these pleadings and at trial challenging." App.93–94. It observed that the government's prosecution of "off-label marketing … criminaliz[es] conduct that it is not entirely clear Congress intended to criminalize" and opined that "the statutory and regulatory scheme needs to be rethought." App.94. At sentencing, the court reiterated that the scheme is

"problematic" and "murky," JA2568, but upheld Petitioners' convictions.

Nearly two years after oral argument, the First Circuit affirmed. App.1. The court sought to distinguish the Second Circuit's decision in *Caronia*, which had held that the government cannot prosecute truthful off-label promotion consistent with the First Amendment. App.25–30. The court also rejected Petitioners' due process argument that the "wide array of evidence [that] may be used to support a finding of 'intended use'" imposes no "limiting standards" on "the government's authority to prosecute violations" and deprives regulated parties of "fair notice of the conduct prohibited." App.48.

REASONS FOR GRANTING THE PETITION

The district court correctly recognized that the "statutory and regulatory scheme" prohibiting off-label promotion "needs to be rethought." App.94. This petition offers the Court an ideal vehicle to address the existing scheme's fatal constitutional flaws.

Off-label use is not only lawful, but also common and often critical to patient care. FDA's effort to suppress truthful, non-misleading manufacturer speech about off-label uses is government paternalism at its worst. As the Second Circuit held in *Caronia*, suppressing truthful off-label promotion imposes unconstitutional content- and speaker-based burdens on protected speech. 703 F.3d at 165–69. Muzzling manufacturers also harms doctors and patients, who need more, not less, truthful information about lawful off-label uses. The First Circuit's contrary decision conflicts with *Caronia*. Making matters worse, the

First Circuit also found no due process problem with the government's essentially limitless definition of "intended use" (*i.e.*, "objective intent"), which allows the government to prosecute someone based on the sale of a lawful device with knowledge that doctors lawfully use it off-label. Most devices (and drugs) are used off-label at least some of the time, so most manufacturers have that knowledge. FDA's "intended use" regulations thus effectively criminalize the entire industry. By refusing to draw an enforceable legal line that manufacturers can identify and rely on, FDA exposes untold numbers of people and companies to arbitrary enforcement without fair notice. Individually and together, these constitutional defects chill a broad array of beneficial communications and medical practices.

This petition, therefore, cleanly presents extraordinarily important constitutional questions about which the courts of appeals disagree. This Court should grant review.

I. Prohibiting speech about and knowledge of off-label uses violates the Constitution.

Petitioners' prosecution violated the First and Fifth Amendments. Petitioners were convicted based on (1) truthful speech about a lawful off-label use of their lawful device and (2) evidence internal to the company about known off-label uses, which will exist any time a company sells a product that doctors use off-label. The first category of evidence highlights the First Amendment problem of criminalizing the flow of truthful information between manufacturers and doctors. The second highlights the due process problems of arbitrary enforcement, lack of notice, and

the sheer irrationality of criminalizing knowledge of lawful and ubiquitous conduct like off-label use.

A. Prohibiting truthful speech about off-label uses violates the First Amendment.

1. FDA's intended-use regulations allow the government to base an off-label promotion prosecution exclusively on protected speech. Those regulations provide that a new "intended use" may be created by "expressions," such as "labeling claims, advertising matter, or oral or written statements." 21 C.F.R. §§ 201.128, 801.4. That is true even if, as here, those "expressions" are not false or misleading in any respect.

But truthful "[s]peech in aid of pharmaceutical marketing … is a form of expression protected by the Free Speech Clause of the First Amendment." *Sorrell v. IMS Health Inc.*, 564 U.S. 552, 557 (2011). Indeed, "[a] consumer's concern for the free flow of commercial speech often may be far keener than his concern for urgent political dialogue." *Id.* at 566 (cleaned up). "That reality has great relevance in the fields of medicine and public health, where information can save lives." *Id.*

As a result, a law that "imposes a speaker- and content-based burden on" medical-product marketing is subject to "heightened scrutiny." *Id.* at 571. In *Sorrell*, this Court "subjected to heightened judicial scrutiny" a statute that prohibited pharmacies and pharmaceutical manufacturers from selling, disclosing, or using certain prescribing information "for marketing purposes." *Id.* at 557. The statute was content-based because it "disfavor[ed] marketing" and

speaker-based because it "disfavor[ed] … pharmaceutical manufacturers." *Id.* at 564. That was "almost dispositive," the Court held, because "[c]ontent-based regulations are presumptively invalid." *Id.* at 571 (cleaned up). But even assuming that a "different analysis applies" to content-based burdens on "commercial speech," the statute still could not survive scrutiny. *Id.* at 571–72; *see also Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 366 (2002) (invalidating FDCA provision prohibiting advertisements of lawful compounded drugs).

The prohibition of truthful speech about off-label uses through the intended-use regulations likewise violates the First Amendment. *Caronia*, 703 F.3d at 168; *Amarin*, 119 F. Supp. 3d at 205; *Wash. Legal Found.*, 13 F. Supp. 2d at 57–58. The prohibition is "content-based" because "speech about the government-approved use of drugs [and devices] is permitted, while certain speech about the off-label use of drugs [and devices] … is prohibited." *Caronia*, 703 F.3d at 165. And the prohibition is "speaker-based because it targets one kind of speaker—[medical-product] manufacturers." *Id.* Doctors and researchers, among others, may speak freely about off-label uses, but manufacturers may not.

The government thus must, but cannot, satisfy "heightened scrutiny." *Id.* Under *Sorrell*, the fact that the prohibition is content- and speaker-based is "all but dispositive." *Id.* at 164 (quoting *Sorrell*, 564 U.S. at 571); *see also Barr v. Am. Ass'n of Political Consultants, Inc.*, 140 S. Ct. 2335, 2346–47 (2020) (plurality op.); *id.* at 2364 (Gorsuch, J., joined by Thomas, J., concurring) (five Justices agreeing that

content-based regulation of commercial debt-collection calls was subject to strict scrutiny); *Int'l Outdoor, Inc. v. City of Troy*, 974 F.3d 690, 703 (6th Cir. 2020) ("regulation of commercial speech that is not content-neutral is still subject to strict scrutiny"). In fact, the "claim to First Amendment protection here is more compelling than in *Sorrell* because this case involves a criminal regulatory scheme subject to more careful scrutiny." *Caronia*, 703 F.3d at 165.

Even under "a special commercial speech inquiry," *Sorrell*, 564 U.S. at 571, the government cannot show that prohibiting truthful speech about off-label uses "directly advances" a "substantial" government interest and is "not more extensive than is necessary to serve that interest," *W. States Med. Ctr.*, 535 U.S. at 367 (quotation omitted). The government claims that prohibiting off-label promotion serves an "interest in preserving the effectiveness and integrity of the FDCA's drug approval process, and an interest in reducing patient exposure to unsafe and ineffective drugs" and devices. *Caronia*, 703 F.3d at 166. But prohibiting truthful speech does not "directly advance" either of these interests. *Id.*

The FDCA's approval process itself "contemplates that approved drugs [and devices] will be used in off-label ways." *Id.* Since "off-label drug [and device] use itself is not prohibited, it does not follow that prohibiting the truthful promotion of off-label drug [and device] usage by a particular class of speakers would directly further the government's goals of preserving the efficacy and integrity of the FDA's drug approval process." *Id.*

Nor can the government prohibit truthful speech as a means of "reducing patient exposure to unsafe and ineffective drugs" and devices. *Id.* As long as off-label use is legal and the manufacturer's speech is truthful, the FDCA requires FDA to trust that physicians will appropriately balance the risks and benefits of particular off-label treatments. 21 U.S.C. § 396. "[I]t is the physician's role to consider multiple factors, including a [drug or device's] FDA-approval status, to determine the best course of action for her patient." *Caronia*, 703 F.3d at 167. "[P]rohibiting off-label promotion by a [medical-product] manufacturer while simultaneously allowing off-label use 'paternalistically' interferes with the ability of physicians and patients to receive potentially relevant treatment information." *Id.* at 166.

Such paternalism, anathema to the First Amendment in all circumstances, is especially unjustified when the recipients of speech are doctors, "a highly educated, professionally-trained and sophisticated audience." *Wash. Legal Found.*, 13 F. Supp. 2d at 63; *accord Sorrell*, 564 U.S. at 577. The government cannot restrict advertisements "on the questionable assumption that doctors would prescribe unnecessary" treatments based on truthful, non-misleading speech. *W. States Med. Ctr.*, 535 U.S. at 374. The government has no legitimate interest in "preventing the dissemination of truthful commercial information in order to prevent members of the public from making bad decisions with the information." *Id.*; *see also Sorrell*, 564 U.S. at 577 ("[T]he 'fear that people would make bad decisions if given truthful information' cannot justify content-based burdens on speech."). Particularly "in the fields of medicine and

public health, 'where information can save lives,' it only furthers the public interest to ensure that decisions about the use of prescription drugs [and devices], including off-label usage, are intelligent and well-informed." *Caronia*, 703 F.3d at 167.

The government also has "[n]umerous, less speech-restrictive alternatives" to advance its claimed interests. *Id.* If the government worries that off-label uses undermine the FDCA's approval process, it could limit off-label prescriptions through "ceilings or caps," or even "prohibit … off-label use altogether." *Id.* at 168. The government could also "develop its warning or disclaimer systems," "develop safety tiers within the off-label market," or require "manufacturers to list all applicable or intended indications when they first apply for FDA approval." *Id.* And the government may always prohibit *false* or *misleading* promotion, which alone goes far toward avoiding genuinely unsafe or ineffective treatments. *Amarin*, 119 F. Supp. 3d at 228.

2. Petitioners' prosecution exemplifies how the intended-use regulations suppress and punish truthful and non-misleading speech protected by the First Amendment. The jury here was instructed that "[t]ruthful, non-misleading speech" could be "used … to determine whether the government has proved each element of each offense beyond a reasonable doubt." CA1 Facteau Addendum ("Add.") 73–74. The government introduced extensive evidence of Petitioners' and Acclarent's protected speech, App.109–23, and closed its presentation to jurors by urging them "think about the promotional materials … every piece of promotional material, everything you

heard about how they practiced selling this drug," D. Ct. Dkt. 468 at 113–14; *see id.* at 126–36.[8]

All that speech was truthful and non-misleading, as the jury found by rejecting the government's allegations of fraud and deceit. App.20, 100; JA453–69. Therefore, the *only* speech supporting Petitioners' convictions was truthful, non-misleading speech entitled to First Amendment protection. Because their prosecution subjected that speech to content- and speaker-based burdens, it violated the First Amendment. *Caronia*, 703 F.3d at 168; *Amarin*, 119 F. Supp. 3d at 205.

3. The First Circuit avoided that conclusion by holding that the government used Petitioners' speech merely as *evidence* of a crime. App.24–28. As *Caronia* recognized, however, that is a semantic dodge. 703 F.3d at 160–62. When speech transforms a lawful sale of a device into a crime, the speech is itself the "*actus reus*," not merely evidence of some *other* crime. *Amarin*, 119 F. Supp. 3d at 226–28; *see Holder v. Humanitarian Law Project*, 561 U.S. 1, 28 (2010) (holding that a law "directed at conduct" must satisfy heightened scrutiny if "the conduct triggering coverage under the statute consists of communicating a message"). Confirming this point, the FDCA prohibits not only "[t]he introduction or delivery for introduction into interstate commerce" of an adulterated or misbranded product, but also "[t]he adulteration or misbranding" of a product already "in

[8] In opposing Petitioners' post-trial motions, the government argued they "caused the distribution of the [device] for [an off-label purpose] *by making external marketing claims*." D. Ct. Dkt. 497 at 28 (emphasis added).

interstate commerce." 21 U.S.C. § 331(a)–(b). Once a manufacturer has shipped its product, truthful speech alone could render it adulterated or misbranded.

Here, it was lawful for Acclarent to sell the Stratus device and lawful for doctors to use it off-label. On the government's view, truthful speech about that lawful use transformed the lawful sale of the device into a crime. Using speech as "evidence" for that purpose is functionally no different from criminalizing the speech. *Amarin*, 119 F. Supp. 3d at 226–28. So "the proscribed conduct for which [Petitioners] w[ere] prosecuted was precisely [their] speech in aid of [medical-product] marketing." *Caronia*, 703 F.3d at 162. Anyway, the government need not openly *ban* speech to unconstitutionally *burden* it. The "distinction between laws burdening and laws banning speech is but a matter of degree," so "the Government's content-based burdens must satisfy the same rigorous scrutiny as its content-based bans." *Sorrell*, 564 U.S. at 565–66 (cleaned up). The statute in *Sorrell* likewise burdened speech in aid of medical-product marketing rather than expressly prohibiting it, but that distinction made no constitutional difference. *Id.*

The same is true here. Under the intended-use regulations, the government does not treat just any speech as evidence of intended use. It specifically relies on speech *by manufacturers*—and *only* manufacturers—that concerns *off-label uses*. By choosing which speech it will treat as evidence of intended use based on its own value judgments, the government imposes speaker- and content-based burdens on protected speech. *See*, *e.g.*, *Virginia v.*

Black, 538 U.S. 343, 366 (2003) (rejecting statute's presumption of intent arising from expressive activity). Those "burdens" must satisfy heightened scrutiny no less than "laws banning speech." *Sorrell*, 564 U.S. at 565–66 (cleaned up). That the government has not been so ham-handed as to directly and expressly prohibit truthful off-label promotion is irrelevant. The government may not selectively burden speech it disfavors while exempting speech it favors. *Id.*; *see, e.g.*, *R.A.V. v. City of St. Paul*, 505 U.S. 377, 392 (1992) (invalidating ordinance prohibiting only "fighting words" that "contain … messages of 'bias-motivated' hatred"); *Ark. Writers' Project, Inc. v. Ragland*, 481 U.S. 221, 229–30 (1987) (invalidating sales tax for general-interest magazines that exempted certain publications based on content).

The First Amendment violation here is not affected by the First Circuit's finding that the government introduced evidence in addition to Petitioners' speech. The jury instructions allowed Petitioners to be convicted based on their speech, which violates the First Amendment no matter what other evidence the government may have introduced. The government has never claimed that its other evidence rendered that violation harmless—and for good reason, as the jury may well have convicted Petitioners at least in part based on their protected speech. *Cf. Dawson v. Delaware*, 503 U.S. 159, 168–69 (1992) (holding that introduction of irrelevant evidence of defendant's Aryan Brotherhood membership at sentencing violated the First Amendment and concluding that "harmless error is not before us at this time").

The First Circuit erred in relying on this Court's decision in *Wisconsin v. Mitchell*, 508 U.S. 476 (1993), to reject Petitioners' First Amendment objections. *Mitchell* upheld a statute enhancing the maximum sentence for race-motivated crimes. But it did so for reasons that do not apply here. The statute was not "explicitly directed at expression" but at the subjective "motive" for committing acts that were *already* illegal for speech-independent reasons. *Id.* at 487. The statute also regulated the punishment for separately defined crimes, and "[t]raditionally, sentencing judges have considered a wide variety of factors in addition to evidence bearing on guilt in determining what sentence to impose on a convicted defendant." *Id.* at 485. Here, by contrast, the intended-use regulations expressly target manufacturers' "expressions," 21 C.F.R. §§ 201.128, 801.4, for the purpose of determining their "objective intent" and distinguishing lawful from unlawful conduct. Unlike the traditional use of motive evidence at sentencing, there is no similar history of using speech as the "*actus reus*" that renders otherwise legal conduct a crime. *Amarin*, 119 F. Supp. 3d at 226–28.

The First Circuit emphasized *Mitchell*'s statement that the First Amendment "does not prohibit the evidentiary use of speech to establish the elements of a crime or to prove motive or intent," 508 U.S. at 489. App.24. But, as explained, the intended-use regulations do not use speech as evidence of some *other* criminal act. Mitchell's battery was already a crime regardless of his motivation, but Petitioners' sale of the Stratus was lawful—until truthful speech about off-label use transformed it into a crime. And even if the government *were* merely using speech as

evidence, it is selecting that evidence based not on general grounds of "relevanc[e], reliability, and the like," *Mitchell*, 508 U.S. at 489, but on value judgments about the content of the speech and the identity of the speaker. Nothing in *Mitchell* blesses such a content- and speaker-based use of protected speech.

In addition, the government's prohibition of off-label speech has a far greater "chilling effect" than the "attenuated and unlikely" burden in *Mitchell*. *Id.* at 488–89. In *Mitchell*, the only conceivable chill was the far-fetched "prospect of a citizen suppressing his bigoted beliefs for fear that evidence of such beliefs will be introduced against him at trial if he commits a more serious offense against person or property." *Id.* But under the intended-use regulations, the only conduct other than speech that is required to trigger criminal liability is the lawful distribution of an FDA-approved product. As a result, every manufacturer must worry that truthful speech about its products could render them contraband. That is a direct, nonspeculative burden that chills truthful speech about lawful off-label uses of lawful products. Brief of Members of the Medical Information Working Group as *Amici Curiae* at 1–2 (1st Cir.).

B. The intended-use regulations violate the Fifth Amendment.

The First Circuit also upheld Petitioners' convictions on the ground that the government introduced evidence of intended use other than Petitioners' protected speech. Far from curing the First Amendment problem, that rationale confirms

that the intended-use regulations *also* violate due process.

1. Given off-label treatment's prevalence and importance to patient care, it is inconceivable that Congress would ban it. In fact, Congress not only has *not* banned off-label use—Congress has forbidden *FDA* from doing so and has required federal healthcare programs to pay for many off-label uses. *Supra* p. 3. It would be even more irrational to criminalize *knowledge* of off-label use while permitting off-label use itself. Yet FDA's intended-use regulations do precisely that by providing that an unlawful off-label intended use "may be shown … by circumstances in which the article is, with the knowledge of such persons or their representatives, offered or used for a purpose for which it is neither labeled nor advertised." 21 C.F.R. §§ 201.128, 801.4.

This regime makes no sense and is a recipe for arbitrary enforcement. Most FDA-approved products are used off-label at least some of the time, and manufacturers know as much simply by complying with their obligation to monitor the use of their products for potential adverse events. If the intended-use regulations mean what they say, then most manufacturers commit a crime by selling most FDA-approved products. The government has tied itself in knots, in this case and over the decades, to avoid grappling with this untenable reality. So did the district court here. Its instructions told the jury that "[m]ere knowledge that doctors are using a device for purposes other than its labeled use does not give rise to a new intended use." Add.74. But the instructions did not tell the jury what, beyond "[m]ere knowledge"

of off-label use, *would* give rise to an off-label intended use—other than "[o]ff-label promotional statements," with all the First Amendment problems that entails. *Id*. Moreover, in the same breath that the instructions told the jury that knowledge of off-label use was not enough to convict, the instructions told the jury the exact opposite: an off-label intended use "may be shown by the circumstances that the device is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised." *Id.*

Similarly, the court instructed the jury that "[m]erely distributing a device with knowledge that it will be used for a use other than the use cleared or approved by the FDA is not fraudulent or illegal." Add.73. Again, however, the court did not tell the jury what "more" was supposedly required. And again, the court told the jury the opposite in the very next sentence: "That being said, if a manufacturer has received 510(k) clearance to distribute a device for one intended use, it may not distribute the device for a significantly different intended use unless it obtains a new 510(k) clearance or a PMA approval for the device with that new intended use." *Id*. In other words, it *is* illegal after all to distribute an FDA-cleared device where knowledge of an off-label use makes that use intended. The Fifth Amendment prohibits the government from playing these word games with citizens' liberty.

As shown by the emptiness of these efforts to make the intended-use regulations seem less all-encompassing than their language provides, the fundamental problem with this regime is that the

regulations make it a crime to distribute an FDA-approved product based on nothing more than knowledge that it is used off-label. The government and the courts below thus gestured at atextual limitations of the regulations' language that they then immediately took back. The upshot is that all it takes to make selling an FDA-approved drug or device a crime is knowledge—which the manufacturer cannot avoid—of off-label use—which is entirely lawful.

That regime violates due process. An "expansive," industry-wide prohibition on sales of medical products with off-label uses "raise[s] significant constitutional concerns" because it criminalizes vast swaths of "commonplace" conduct. *McDonnell v. United States*, 579 U.S. 550, 574–76 (2016). This principle, along with the "related" prohibition of vague criminal statutes, sounds in fair notice and citizens' right to be protected from arbitrary government conduct. *Id.* at 574–76; *see United States v. Kozminski*, 487 U.S. 931, 949–50 (1988); *cf. Wooden v. United States*, 595 U.S. 360, 390 (2022) (Gorsuch, J., concurring) ("'[P]enal laws are to be construed strictly' because of 'the tenderness of the law for the rights of individuals'—and, more specifically, the right of every person to suffer only those punishments dictated by 'the plain meaning of words.'" (quoting *United States v. Wiltberger*, 18 U.S. (5 Wheat.) 76, 95–96 (1820))). When a criminal prohibition imposes a "standardless sweep" on regulated conduct, then regulated parties "could be subject to prosecution, without fair notice, for the most prosaic interactions." *McDonnell*, 579 U.S. at 576 (cleaned up).

Such an all-encompassing criminal prohibition "inject[s] arbitrariness into the assessment of criminal liability," *Van Buren v. United States*, 141 S. Ct. 1648, 1662 (2021), and empowers the government to pick and choose whom to prosecute. When a law makes everyone a criminal, only the unreviewable discretion of prosecutors determines who is and is not imprisoned for the same conduct. The Due Process Clause does not allow the government to leave potential defendants "at the mercy of *noblesse oblige*" in this way. *FCC v. Fox Television Stations, Inc.*, 567 U.S. 239, 255 (2012) (quoting *Untied States v. Stevens*, 559 U.S. 460, 480 (2010)). Instead, "[t]o satisfy due process, a penal statute must define the criminal offense … in a manner that does not encourage arbitrary and discriminatory enforcement." *Skilling v. United States*, 561 U.S. 358, 402–03 (2010) (cleaned up).

The intended-use regulations fail that test. To begin, "objective intent" is an oxymoronic construct that that has "no direct parallels in either tort law or criminal law." Gregory Gentry, *Criminalizing Knowledge: The Perverse Implications of the Intended Use Regulations for Off-Label Promotion Prosecutions*, 64 Food & Drug L.J. 441, 443 (2009).[9] The government itself has struggled to define the phrase, repeatedly flip-flopping over the years and across cases over whether it encompasses or is somehow distinct from

[9] The First Circuit said "objective intent" is "a familiar and well-established concept," but it cited no other context in which that concept appears. App.49. The only case it cited involved ordinary *subjective* intent. *United States v. Williams*, 553 U.S. 285, 306 (2008).

the more familiar concept of *subjective* intent. *Compare* JA258 (FDA claiming "intended use" is "determined with reference to marketing claims"); JA189 ("FDA interprets intent to be objective intent. It's not subjective intent."); JA192 (arguing subjective intent "does not meet the objective intent[] standard"), *with* JA618 n.3 (claiming "intended use … can be established not only by … subjective claims of intent, but also by objective evidence"). And the intended-use regulations, far from clearly distinguishing between permissible and prohibited conduct, contain language that naturally covers essentially the entire medical-product industry. In addition to guaranteeing arbitrary enforcement, that regime is flat-out irrational. There is no "conceivable [rational] basis," *FCC v. Beach Commc'ns, Inc.*, 508 U.S. 307, 315 (1993), for criminalizing the sale of FDA-approved products based on manufacturers' knowledge that those products will be used in an entirely legal way.

To preserve its unlimited discretion, the government has refused to draw an ascertainable, legally meaningful line to identify when off-label intended uses are deemed to exist. Instead, FDA has issued a series of non-binding "guidance" documents addressing certain circumstances in which FDA generally "intends" to exercise its discretion not to take enforcement action. *E.g.*, JA238 (FDA guidance stating it does "not create or confer any rights" and does "not operate to bind FDA"); *accord* 21 C.F.R. § 10.115(d)(1). These guidances confirm, rather than solve, the due process problems posed by the seemingly limitless breadth of the intended-use regulations.

First, guidance about enforcement discretion presupposes that the conduct at issue violates the law; otherwise, there's nothing to enforce in the first place. FDA's guidances thus underscore the breadth of its intended-use regulations. Second, the government cannot satisfy due process through non-binding guidance that it can follow or ignore as it wishes. *City of Chicago v. Morales*, 527 U.S. 41, 60–64 (1999). Citizens have a right to know what the law is and an opportunity to conform their conduct to it—not to be told that their conduct is illegal but that they shouldn't worry because the government "intends" to be reasonable. That is why this Court has consistently refused to "uphold an unconstitutional statute merely because the Government promise[s] to use it responsibly." *United States v. Stevens*, 559 U.S. 460, 480 (2010). Third, even on their own terms, FDA's guidances do not provide adequate clarity. The guidances conceptually distinguish between off-label "promotion" and off-label "scientific exchange." *Supra* pp. 7–8. But these terms are not defined in any statute or regulation, and FDA has never clearly explained what they mean. If there is a line separating the guilty from the innocent—or at least the guilty who are likely to be targeted from the guilty who are probably safe—that line resides in the minds of FDA officials and federal prosecutors, not in any law. *Cf. Johnson v. United States*, 576 U.S. 591, 598 (2015) ("repeated attempts and repeated failures to craft a principled and objective standard" confirm a law's "hopeless indeterminacy").

This state of affairs cannot persist. It is convenient for the government to create a regime in which everyone is guilty and no one knows what will

get them prosecuted. But doing so replaces the rule of law with a rule of prosecutorial discretion that should be intolerable in a free society.

C. These constitutional issues are exceptionally important.

The government's unconstitutional approach to regulating off-label intended uses and truthful speech cries out for this Court's review. The medical-product industry invests billions of dollars every year in investigating new treatments. Brief of PhRMA and Chamber of Commerce of the U.S. as Amici Curiae at 1 (1st Cir.) ("PhRMA Amicus Br."). Subjecting nearly everyone in that industry to a constant threat of prosecution chills valuable speech and conduct by manufacturers and impairs doctors' ability to treat their patients.

Doctors seeking the best treatments for their patients naturally want truthful information about off-label uses. *Caronia*, 703 F.3d at 167. The best source of such information is often the manufacturer, which naturally knows more than anyone else about its products. But the government's prohibition of off-label promotion chills the provision of such information. Without any reliable way to determine which speech will be deemed unlawful "promotion," manufacturers self-censor, forgoing truthful communications that would benefit doctors and their patients. PhRMA Amicus Br. at 5–6; *cf. Minn. Voters All. v. Mansky*, 585 U.S. 1, 16–17 (2018) (invalidating "expansive" ban on "political" attire at polling sites for failure to "articulate some sensible basis for distinguishing what may come in from what must stay out"); *Young Israel of Tampa, Inc. v. Hillsborough*

Area Regional Transit Auth., 89 F.4th 1337, 1347–48 (11th Cir. 2024) (invalidating ban on "religious" bus ads that "fails to define key terms, lacks any official guidance, and vests too much discretion in those charged with its application").

In this case, otolaryngologists uniformly testified that treating sinus conditions with steroids is common and often the standard of care. *Supra* p. 9. So Petitioners were convicted for knowing and providing truthful information about a common, medically accepted off-label use of an FDA-cleared device. *See* JA1101 (arguing for guilt because Petitioners knew Stratus was "used by doctors to deliver Kenalog-40"). The government's regime thus "legalizes the outcome—off-label use—but prohibits the free flow of information that would inform that outcome." *Caronia*, 703 F.3d at 167. That harms the public health. *See Wash. Legal Found.*, 13 F. Supp. 2d at 67.

Because of the intended-use regulations' irrational and indeterminate scope, the chill extends beyond speech to common and beneficial practices in the medical-product industry. Manufacturers commonly take an "iterative" approach to FDA approval, seeking clearance for a limited use and then seeking expanded clearances in future submissions. *Supra* p. 9. It is also common for manufacturers to want to research and develop potential new uses for products cleared for other uses. Those practices benefit doctors and patients by allowing for earlier approval of drugs and devices, facilitating the development of new treatments, and generating scientific information that can assist doctors' treatment decisions.

The intended-use regulations, as even the district court recognized, chill those beneficial practices. *See* JA829 (acknowledging threat to "this approval strategy which is that you get the 510(k) for some little use and then you get it out in the market"). As supposed proof of Petitioners' crimes, the government introduced evidence of Acclarent's intent to seek progressive clearances for the Stratus based on iterative 510(k) submissions. *E.g.*, JA2316–19. The government also introduced evidence that Acclarent had studied the possibility of using the Stratus with steroids. *E.g.*, JA1102A, 1839A–39B. The message this sends is that sometimes the government will allow manufacturers to seek iterative FDA approvals and research additional uses, and sometimes the government will prosecute you based on that conduct. And there is no way to know if you have crossed the government's unexplained line until you're indicted. Facing that risk, manufacturers will stop innovating, limiting the development of new treatments. MDMA Comment at 4.

As if all that were not enough, other legal rules make the intended-use minefield even more perilous. First, misdemeanor misbranding and adulteration are strict-liability offenses. 21 U.S.C. §§ 331, 333(a)(1). The lack of any "scienter requirement" exacerbates the lack of "notice" of what "conduct is proscribed." *Vill. of Hoffman Ests. v. Flipside, Hoffman Ests., Inc.*, 455 U.S. 489, 499 (1982). Second, under the "responsible corporate officer" doctrine, an officer can be found guilty for subordinates' misconduct even if he did not participate in it, direct it, or even know about it, as long as he had the responsibility and authority to prevent or correct the violation. *See United States v.*

Park, 421 U.S. 658, 676 (1975). Finally, the penalties for even a misdemeanor conviction are severe. If a company is convicted of misbranding or adulteration, it can be excluded from Medicare and Medicaid, 42 U.S.C. § 1320a-7—a "death knell" for a medical-product company. App.94.

And all this for a crime that Congress did not create. It is FDA's intended-use regulations that make criminals of manufacturers that speak truthfully about their FDA-approved products. Even the district court recognized the tenuous nature of the government's criminal theories: "the Government continues to prosecute the conduct by patching together the misbranding and adulteration regulations, thereby criminalizing conduct that it is not entirely clear Congress intended to criminalize." App.94. The FDCA's "misbranding" and "adulteration" provisions are too thin a reed to support FDA's creation of a regulatory crime that effectively outlaws the entire medical-product industry. *See West Virginia v. EPA*, 597 U.S. 697, 721–23 (2022).[10]

The district court and First Circuit themselves recognized the importance of the issues presented by this case. The district court took *four years* to decide Petitioners' post-trial motions because it "f[ound] the issues … challenging." App.93–94. The court found it "clear that the statutory and regulatory scheme needs

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[10] Section 396 states that its injunction against FDA interference with the practice of medicine "shall not change *any existing* prohibition on the promotion of unapproved uses of legally marketed devices." 21 U.S.C. § 396 (emphasis added). The italicized language makes clear that this provision merely begs the question of whether any such promotion prohibition exists.

to be rethought," App.94, and said it "sort of lie[s] in bed at night and think[s] if we can't figure out the law, maybe there is a due process problem," JA1976–77. The First Circuit then took another two years to resolve Petitioners' appeal, with one judge stating at oral argument that "this is obviously a case of great complexity and importance." *See* Oral Argument at 20:35, https://www.ca1.uscourts.gov/sites/ca1/files/oralargs/21-1080_20220307.mp3. Such an important case on such important constitutional issues demands this Court's review.

II. The decision below conflicts with the Second Circuit's decision in *Caronia*.

In rejecting Petitioners' First Amendment arguments, the First Circuit refused to follow the Second Circuit's decision in *Caronia*. App.25–30. *Caronia* held that the First Amendment prohibits the government from using the intended-use regulations to "criminalize the promotion of off-label drug use" because doing so "imposes content- and speaker-based restrictions on speech" that fail both "heightened scrutiny" and the "less rigorous intermediate test" for commercial speech. 703 F.3d at 164.

The decision below allowed the government to do what *Caronia* forbade. The First Circuit tried to distinguish *Caronia* on the ground that here the government merely used off-label promotion as evidence, but that is no distinction at all. *Supra* pp. 20–23. The government prosecuted Petitioners based on speech about a lawful off-label use of the Stratus, and the jury found that speech was not false or misleading. App.20, 100. Yet the government and the district court both told jurors they could convict

Petitioners based on that speech. *E.g.*, Add.73–74; D. Ct. Dkt. 468 at 113–36. That violated the First Amendment, and the First Circuit's contrary holding conflicts with *Caronia*.

The First Circuit also distinguished *Caronia* because the government introduced evidence in addition to Petitioners' speech, but that is irrelevant to the First Amendment issue. Because the jury may well have relied on truthful speech in convicting Petitioners, a new trial is required at the very least. *Supra* p. 22.

In any event, the government's additional evidence only goes to show that the prosecution violated the Fifth Amendment *as well as* the First Amendment. As explained above, allowing a conviction based on knowledge of off-label use—or knowledge plus protected speech—violates due process. That the government violated more constitutional rights in this case than in *Caronia* is not a point in its favor.

III. The Court should grant review in this case.

This case presents an ideal vehicle for the important questions presented. It presents both the First Amendment and Fifth Amendment defects with the intended-use regulations, allowing the Court to consider them together in one case. And those issues are presented cleanly. Because the jury found that Petitioners' speech was not false or misleading, this case cleanly presents the question whether the government may use the intended-use regulations to suppress truthful, non-misleading speech about lawful off-label uses. The government's and the First

Circuit's reliance on evidence of Petitioners' knowledge cleanly presents the Fifth Amendment issues. And although the intended-use regulations were amended in 2021, those non-substantive amendments "clarifie[d] but d[id] not change FDA's interpretation and application of existing intended use regulations for medical products." 86 Fed. Reg. at 41,399. The constitutional issues presented in this case have not changed since Petitioners' convictions.

Although these issues are important and affect thousands of manufacturers, doctors, and patients every day, this Court will have few, if any, other opportunities to address them. Due to the intended-use regulations' boundless scope and the severe penalties, defendants being investigated for off-label promotion rarely can take the risk of litigating their cases and instead are forced to plead guilty or settle. Similarly, declaratory-judgment actions filed by manufacturers against the government have not been litigated to final judgment, as the government routinely settles such actions to avoid judicial scrutiny of the intended-use regime. For example, when Allergan sought a declaration that the First Amendment entitled it to share truthful information about off-label uses, the government got Allergan to dismiss its action as part of a resolution of retrospective investigations.[11] And after the court in *Amarin* preliminarily enjoined an enforcement action

[11] *See* Press Release, DOJ, Allergan Agrees to Plead Guilty and Pay $600 Million to Resolve Allegations of Off-Label Promotion of Botox® (Sept. 1, 2010), https://tinyurl.com/4uedtrdm.

against Amarin's off-label speech, the government avoided future proceedings by settling.[12]

This is, therefore, one of the few "off-label promotion" cases that will ever last long enough to reach this Court's docket. If the Court does not take this opportunity to review the important constitutional issues raised in this petition, it may not get another—and the chilling of valuable speech and the liberty and rule-of-law harms of a regime that invites arbitrary enforcement will persist.

CONCLUSION

This Court should grant the petition for certiorari.

Respectfully submitted,

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March 13, 2024

[12] *See* Press Release, Amarin's Right to Promote Vascepa® Off-Label Affirmed Under First Amendment Litigation Settlement Terms (Mar. 9, 2016).