CASE NO. 21-1080

IN THE

United States Court of Appeals

FOR THE FIRST CIRCUIT

UNITED STATES

Appellee,

v.

WILLIAM FACTEAU

Defendant-Appellant.

On Appeal From the United States District Court for the District of Massachusetts
(Case No. 1:15-cr-10076, Hon. Allison D. Burroughs)

BRIEF OF MEMBERS OF THE MEDICAL INFORMATION WORKING GROUP AS *AMICI CURIAE* IN SUPPORT OF REVERSAL

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RULE 26.1 DISCLOSURE STATEMENT

The undersigned counsel certifies that the following members of the Medical Information Working Group (MIWG), a private non-governmental entity comprised of major manufacturers of prescription drugs, biopharmaceutical products, and medical devices, are submitting this brief as amici curiae: Amgen Inc., Biosplice Therapeutics, Inc., Boehringer Ingelheim Pharmaceuticals, Inc., Bristol Myers Squibb Company, Eli Lilly and Company, GlaxoSmithKline LLC, Novartis Pharmaceuticals Corporation, and Pfizer Inc.

Based on the company's review of publicly available information, Amgen Inc. is a corporation with publicly traded stock of which no publicly traded corporation owns more than 10%.

Biosplice Therapeutics, Inc. is a privately held company of which no publicly traded corporation owns more than 10%.

Boehringer Ingelheim Pharmaceuticals, Inc. is the largest U.S. subsidiary of Boehringer Ingelheim Corporation and is part of the Boehringer Ingelheim group of companies. Neither entity is publicly traded.

Bristol Myers Squibb Company is a publicly held corporation and no publicly held corporation owns more than 10% of its outstanding stock.

Based on the company's review of publicly available information, Eli Lilly and Company is a corporation with publicly traded stock of which no publicly traded corporation owns more than 10%.

GlaxoSmithKline LLC is a Delaware limited liability company and the U.S. operating company for GlaxoSmithKline, a science-led global healthcare company. GlaxoSmithKline LLC is owned, through several layers of wholly-owned subsidiaries, by GlaxoSmithKline plc, a publicly-traded public limited company organized under the laws of England. GlaxoSmithKline plc has no parent company, and no publicly traded corporation owns 10% or more of its outstanding shares.

Novartis Pharmaceuticals Corporation is an indirect, wholly owned subsidiary of Novartis AG, which trades on the SIX Swiss Exchange under the ticker symbol NOVN and whose American Depository Shares are publicly traded on the New York Stock Exchange under the ticker symbol NVS.

Pfizer Inc. is a corporation with publicly traded stock of which no publicly traded corporation owns more than 10%.

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INTERESTS OF AMICI CURIAE

Members of the Medical Information Working Group (MIWG) respectfully submit this *amici curiae* brief to assist the Court in resolving the important constitutional and statutory issues presented by this appeal.[1]

MIWG is an informal working group of manufacturers of biopharmaceutical products and medical devices. MIWG was formed in 2006 to improve the regulatory framework and enforcement climate affecting manufacturers' dissemination of information about their products, including information about "off-label" uses of lawfully marketed products. MIWG and its members have made numerous submissions to the Food and Drug Administration (FDA), including petitions seeking clarification of, and substantive changes to, the existing regulatory framework.[2]

In particular, MIWG has raised concerns that the current enforcement scheme is ambiguous and at odds with fundamental First and Fifth Amendment principles that protect manufacturers' ability to engage in truthful and non-misleading communications about off-label uses of their

[1] Members of MIWG joining this brief include: Amgen Inc., Biosplice Therapeutics, Inc., Boehringer Ingelheim Pharmaceuticals, Inc., Bristol Myers Squibb Company, Eli Lilly and Company, GlaxoSmithKline LLC, Novartis Pharmaceuticals Corporation, and Pfizer Inc.

[2] MIWG's prior briefs and FDA submissions are available at www.miwg.org.

products. The unclear rules that characterize the regulatory framework, and the Government's expansive, ad-hoc approach to enforcement, provide inadequate notice of the line between permissible and impermissible speech and, consequently, manufacturers' constitutionally protected speech is chilled. This chilling effect is compounded by the threat of criminal penalties.

Members of MIWG participated as *amici curiae* in this case below, and also participated in other leading cases addressing constitutional protections for truthful, non-misleading speech about FDA-approved products. *See United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012); *Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 196 (S.D.N.Y. 2015); *Pacira Pharms., Inc. v. FDA*, No. 15-cv-07055 (S.D.N.Y. 2015) (favorably resolved). Accordingly, MIWG brings an important perspective to issues central to this appeal.

STATEMENT OF COMPLIANCE WITH RULE 29(A)

Amici obtained consent to file this brief from Appellee the United States and Defendants-Appellants William Facteau and Patrick Fabian.

This brief is submitted pursuant to Rule 29 of the Federal Rules of Appellate Procedure and First Circuit Rule 29(A)(4)(e). No party or party's counsel authored this brief in whole or in part; no party or party's counsel contributed money to fund the preparation or submission of this brief; and no person except *amici curiae*, their members, or their counsel contributed money intended to fund the preparation or submission of this brief.

INTRODUCTION AND SUMMARY OF THE ARGUMENT

As the court below explained, "there is no statute that specifically prohibits off-label marketing and yet 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." *United States v. Facteau*, No. 15-cr-10076, 2020 WL 5517573, at *1 (D. Mass. Sept. 14, 2020).

This strategy is not constitutionally permissible. Regulations of speech, such as the FDA's regulatory regime governing manufacturer communications about medical products, must be clear and precise to satisfy the Due Process Clause of the Constitution. The government must provide regulated parties with "fair notice of conduct that is forbidden or required." *FCC v. Fox Television Stations, Inc.*, 567 U.S. 239, 253 (2012). Due process standards are particularly stringent for criminal regulation of speech to ensure that ambiguity does not chill protected speech. And, as numerous courts (including the district court below) have recognized, the First Amendment protects truthful and non-misleading speech about medical products even when such speech is "off-label." *Caronia*, 703 F.3d 149; *Facteau*, 2020 WL 5517573; *Amarin*, 119 F. Supp. 3d 196. Truthful, non-misleading

off-label speech provides valuable information to the medical community and drives innovation and advancements for the benefit of public health.

Despite the sustained efforts of MIWG and other stakeholders to obtain clarity, the regulatory regime governing manufacturer communications remains unclear. For more than a decade, MIWG has requested that FDA clarify the regulatory framework for communicating off-label information. Yet the regime still does not draw clear lines between permissible and impermissible speech.

First, the government has failed to adopt a clear and consistent approach regarding the role that a manufacturer's knowledge of its product's off-label use can play in determining "intended use." Second, although FDA has long recognized various "safe harbors" for certain types of off-label communications, the articulations of these safe harbors offer neither clarity nor certainty. They are largely contained in guidance documents, which are non-binding and in most cases issued only in draft form, raising further First and Fifth Amendment concerns. The safe harbors also do not cover all constitutionally protected off-label communications, and therefore do not obviate the problems with the intended use rule.

The district court acknowledged the serious implications of the lack of clarity in the current framework but nevertheless adopted a broad approach to determining "intended use." The court failed to recognize the constitutionally impermissible chilling effect that the current regime has on manufacturer speech.

The Defendants' convictions under the Federal Food, Drug, and Cosmetic Act (FDCA) implicate these constitutional principles. Under the current, ambiguous regulatory regime, a conviction based on allegations that off-label promotion created a new "intended use" necessarily implicates due process notice issues, for there is no clear rule defining "intended use." As a result, someone in the Defendants' position could not have known in advance whether and to what extent truthful, non-misleading communications about off-label uses were permitted or prohibited.

These problems were exacerbated by the confusing jury instruction regarding the "intended use" standard. Multiple juries could have reached different conclusions regarding the relevance of knowledge to the "intended use" inquiry. It should come as no surprise that a jury of laypersons would have difficulty understanding the regulatory regime and applying ambiguous legal standards to the facts in this case given that FDA and

industry stakeholders cannot align on the correct legal interpretation of "intended use" and the evidence that may be considered as part of this inquiry.

ARGUMENT

I. CRIMINAL LAW RESTRICTIONS ON TRUTHFUL, NON-MISLEADING SPEECH ABOUT MEDICAL PRODUCTS MUST BE CLEAR AND PRECISE TO BE CONSTITUTIONAL.

"[O]ne of the most basic" standards of our justice system is that "no one may be punished ... for failing to conform his conduct to rules that he could not ascertain." *Project B.A.S.I.C. v. Kemp*, 947 F.2d 11, 21 (1st Cir. 1991). That is true especially where speech is involved. The "government may regulate in the area of First Amendment freedoms" only if it provides "the narrow specificity that the Constitution demands." *Brown v. Entm't Merch. Ass'n*, 564 U.S. 786, 807 (2011) (Alito, J., concurring) (internal quotation marks omitted).

This strict standard is driven by "two connected but discrete due process concerns: first, that regulated parties should know what is required of them so they may act accordingly; second, precision and guidance are necessary so that those enforcing the law do not act in an arbitrary or discriminatory way." *Fox Television*, 567 U.S. at 253. The government must

provide regulated parties with "fair notice of conduct that is forbidden or required." *Id.*

"When speech is involved, rigorous adherence to those requirements is necessary to ensure that ambiguity does not chill protected speech." *Id.* at 253-54; *see In re Tam*, 808 F.3d 1321, 1342 (Fed. Cir. 2015) (en banc), *as corrected* (Feb. 11, 2016), *aff'd sub nom. Matal v. Tam*, 137 S. Ct. 1744 (2017) (noting the "uncertainty of speech-affecting standards has long been recognized as a First Amendment problem" and "as a problem under Fifth Amendment vagueness standards as they have been specially applied in the First Amendment setting"); *cf. McDonnell v. United States*, 136 S. Ct. 2355, 2372 (2016) (rejecting a rule that would "cast a pall of potential prosecution" over ordinary political activity, "rais[ing] significant constitutional concerns"). Vague and overbroad regulation is "particularly treacherous" because the threat of criminal sanctions would deter a party "seek[ing] to exercise protected First Amendment rights." *Buckley v. Valeo*, 424 U.S. 1, 76-77 (1976) (per curiam); *see also Keyishian v. Bd. of Regents of the Univ. of N.Y.*, 385 U.S. 589, 604 (1967) (noting that "standards of permissible statutory vagueness are strict in the area of free expression ... because First Amendment freedoms need breathing space to survive") .

These First and Fifth Amendment principles squarely apply to the FDA regulatory regime governing manufacturer communications upon which the Defendants' convictions were predicated. The Supreme Court confirmed a decade ago that speech in aid of medical product marketing is protected by the First Amendment and that restrictions on such speech are subject to heightened judicial scrutiny. *Sorrell v. IMS Health Inc.*, 564 U.S. 552, 557, 566 (2011) (recognizing the importance of First Amendment protection "in the fields of medicine and public health, where information can save lives").

Further, as multiple courts—including the district court below—have recognized, the First Amendment protects truthful and non-misleading speech about medical products even when such speech is "off-label" (*i.e.*, discusses uses of a product not set forth in its FDA-approved or FDA-cleared labeling). *Caronia*, 703 F.3d 149; *Amarin*, 119 F. Supp. 3d 196; *Facteau*, 2020 WL 5517573.

Off-label use of drugs and medical devices is lawful, "widespread in the medical community and often is essential to giving patients optimal medical care." *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350-51 & n.5 (2001); *see Caronia*, 703 F.3d at 166; 21 U.S.C. § 396 (providing that the

FDCA does not "limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease"). The dissemination of up-to-date medical information about a medical product helps to guide treatment decisions and ensures that patients receive care based on current, sound information. Because manufacturers often have the earliest, surest access to new information about their products and have the resources and infrastructure to share this information in a timely and efficient manner, they are well-positioned to provide health care professionals with accurate and up-to-date information, including about "off-label" uses.

The FDCA does "not expressly prohibit or criminalize off-label promotion." *Caronia*, 703 F.3d at 160; *see Facteau*, 2020 WL 5517573, at *1. However, the government contends that a manufacturer's "off-label" speech can render a medical device misbranded under 21 U.S.C. § 352(o), because it triggers the requirement to obtain further clearance for the new "intended use" under 21 U.S.C. § 360(k).[3] Likewise, the government contends that a

[3] The government also argued that a device is misbranded under 21 U.S.C. § 352(f)(1) if it has a new "intended use" for which adequate directions (devised through premarket review) are lacking. The jury here rejected this argument.

device is adulterated, under 21 U.S.C. § 351(f)(1)(B), if it has a new "intended use" that triggers the requirement to obtain premarket approval. But as discussed below, the meaning of "intended use," and thus the line between permissible and impermissible speech in this area, remains highly vague despite the industry's sustained efforts to obtain clarity.

Such problems of vagueness in a speech-regulating regime are particularly concerning where, as in this case, violation carries criminal penalties and the audience consists of sophisticated physicians who rely on accurate, up-to-date medical information to guide patient care. *See Buckley*, 424 U.S. at 76-77; *Sorrell*, 564 U.S. at 577 ("[First Amendment] precepts apply with full force when the audience, in this case prescribing physicians, consists of sophisticated and experienced consumers") (internal quotation marks omitted). Fear of criminal sanctions "may deter those who seek to exercise protected First Amendment rights," *Buckley*, 424 U.S. at 76-77, because "[u]ncertainty" in a speech restriction "contributes significantly to the chilling effect on speech," *Tam*, 808 F.3d at 1342. Because manufacturer communications regarding off-label uses are chilled by the lack of clarity in the regulatory regime, health care professionals and the patients they treat

are deprived of important medical information that would otherwise advance patient care and public health.

As explained in the amicus curiae briefs by PhRMA and WLF, the government's position in this case raises critical issues directly under the First Amendment. MIWG's brief raises an independent set of constitutional arguments, based on the Fifth Amendment's notice requirements, and the court need not address the issues arising under the First Amendment if it reverses the judgment below for the reasons outlined herein or otherwise.

II. THE RULES GOVERNING MANUFACTURER SPEECH REMAIN VAGUE NOTWITHSTANDING INDUSTRY'S SUSTAINED EFFORTS TO OBTAIN CLARITY.

A. MIWG And Other Regulated Parties Have Long Sought to Clarify the Vague Rules Governing Manufacturer Speech.

Despite efforts by MIWG and other stakeholders to obtain clarity, the regulatory regime governing manufacturer communications remains muddled, including by failing to draw clear lines between permissible and impermissible speech. The persistent lack of clarity relating to intended use is perhaps best exemplified by the unclear and inconsistent statements regarding the role that a manufacturer's knowledge of an off-label use can play.

Currently, FDA regulations define "intended use" to mean "the objective intent of the persons legally responsible for the labeling of devices," which "may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives," "the circumstances surrounding the distribution of the article," or evidence that "the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised." 21 C.F.R. § 801.4.

Notwithstanding the reference to "knowledge" in the regulatory definition, the Department of Justice has repeatedly told federal courts that "knowledge" of a product's off-label use is *not* itself a basis for finding that the use is an "intended use."[4] But the government has not adequately

[4] *See, e.g.*, Tr. of Oral Arg. at 10, *United States v. Caronia*, No. 09-5006 (2d Cir. Dec. 2, 2010) (in response to the court asking whether a crime is committed if a person "hasn't promoted but he sent [a drug] out knowing and perhaps intending that it be used for something other than an on-label use," government counsel replied: "I believe not, Your Honor, I don't think that would be a crime"); Defs.' Mem. in Supp. of Mot. to Dismiss or for Summ. J. at 27- 28, *Par Pharm., Inc. v. United States*, No. 11-cv-1820 (D.D.C. Jan. 11, 2012, ECF No. 14-1 (rejecting the view that "knowledge of unapproved uses is sufficient by itself to establish intent"); Defs.' Mem. of P&A in Supp. of Mot. to Dismiss or for Summ. J. at 22, *Allergan v. United States*, No. 09-cv-01879 (D.D.C. Jan. 7, 2010), ECF No. 26-1 ("Allergan is wrong when it suggests that

clarified what role, if any, knowledge plays in determining an "intended use." If knowledge of off-label use—alone or in combination with other unspecified factors—could create a new intended use, it would be nearly impossible for a manufacturer to ensure that its conduct complied with the law. Because off-label uses are common, and FDA requires manufacturers to monitor how their products are used, *see, e.g.*, 21 C.F.R. §§ 314.80, 803.50, 803.52, manufacturers will typically know that their products are sometimes used off-label. Indeed, manufacturers need to know about the likely demand for their products, in order to ensure adequate supply and avoid shortages that could jeopardize public health.

Regulated parties have repeatedly attempted to obtain necessary clarity regarding the government's interpretation and application of the "intended use" regulation, as well as other aspects of the regulatory regime. Over 25 years ago, regulated parties filed citizen petitions urging FDA to promulgate clear, constitutionally appropriate rules, *see* 59 Fed. Reg. 59,820, 59,821 (Nov. 18, 1994), and litigation, *see Wash. Legal Found. v. Kessler*, 880 F.

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it 'commits a crime' . . . if it merely has 'knowledge or notice of an off-label use.'").

Supp. 26, 29 (D.D.C. 1995) (describing FDA's insistence that it "ha[d] not adopted a final agency policy regarding manufacturer distribution of information concerning off-label usage"). In 2002, FDA requested comments on First Amendment issues, including "the extent of FDA's ability to regulate speech concerning off-label uses," *see* 67 Fed. Reg. 34,942, 34,944 (May 16, 2002), but did not clarify the regulatory framework.

For more than a decade, MIWG has requested that FDA clarify the regulatory framework for communicating off-label information. In addition to numerous written submissions, MIWG has met with FDA officials dating back to 2007. Members of MIWG also filed two petitions requesting specific actions and clarifications regarding various rules and policies relevant to FDA's regulation of manufacturer communication about off-label uses. In 2011, the first petition asked that FDA amend the definition of "intended use" and issue additional regulations to clarify that certain types of non-promotional medical and scientific communications could not be used to establish a new intended use.[5] A 2013 petition renewed those concerns

[5] Specifically, this petition requested that FDA adopt legally binding regulations clarifying its policies relating to manufacturer responses to unsolicited requests, scientific exchange, payor communications, and dissemination of third-party clinical practice guidelines.

and also requested that FDA comprehensively review and modify its regulatory framework in view of constitutional and statutory limitations.

In 2014, FDA responded by letter *granting* both petitions. The agency stated that it "plans to issue guidance that addresses unsolicited requests, distributing scientific and medical information on unapproved new uses, and manufacturer discussions regarding scientific information more generally, by the end of [2014]." Letter from Leslie Kux, FDA, to Alan R. Bennett and Joan McPhee, Ropes & Gray LLP, and Coleen Klasmeier and Paul Kalb, Sidley Austin LLP at 9, Docket Nos. FDA-2011-P-0512 and FDA-2013-P-1079 (June 6, 2014) ("June 6 FDA Letter"). Yet seven years later, FDA has still not fulfilled its commitments.

Although FDA initiated rulemaking in 2015 to clarify the definition of "intended use," including the role that "knowledge" can play, this rulemaking remains unfinished. In September 2015, FDA proposed to amend the regulatory definitions of "intended use" for both drugs and devices. FDA explained that changes to these definitions were needed "to reflect how the Agency currently applies them." 80 Fed. Reg. 57,756, 57,756 (Sept. 25, 2015). FDA stated that it will not "regard a firm as intending an unapproved new use for an approved or cleared medical product based

solely on the firm's knowledge that such product was being prescribed or used by doctors for such use." *Id*. at 57,757. Accordingly, FDA proposed to delete the sentence in the regulation stating that "intended use" could be established "if a manufacturer knows, or has knowledge of facts that would give him notice" of a use. *Id.* at 57,764-65; *see* MIWG, PhRMA, & BIO, Petition to Stay and for Reconsideration, Docket No. FDA-2015-N-2002, at 8 (Feb. 8, 2017) ("Petition to Stay"). FDA explained that this deletion "would not reflect a change in FDA's approach regarding evidence of intended use for drugs and devices." *Id*. at 57,761.

In January 2017, FDA issued a final rule that departed dramatically from the proposed rule. 82 Fed. Reg. 2,193 (Jan. 9, 2017). Rather than delete the final sentence of the "intended use" definition, the agency replaced it with an entirely new sentence, setting forth an open-ended standard that a new "intended use" would be created wherever "the totality of the evidence establishes that a manufacturer objectively intends" the use. *Id*. at 2,217. Additionally, the final rule asserted that "FDA's longstanding position is that, in determining a product's 'intended use,' the Agency may look to any relevant source of evidence." *Id.* at 2,206. MIWG, among others, submitted a Petition for Stay and for Reconsideration, on the grounds that the final rule

violated the Administrative Procedure Act, exceeded FDA's statutory authority, and raised significant constitutional issues. *See* Petition to Stay. MIWG explained that, contrary to FDA's assertion, the final rule represented a drastic change in the government's position regarding how to determine "intended use," including with respect to manufacturer knowledge. *See id.* at 18; MIWG, Comments on "Intended Use" Final Rule, Docket No. FDA-2015-N-2002 (July 18, 2017).

Recognizing the potential for confusion resulting from the new language in the 2017 final rule, FDA indefinitely delayed implementation so that the final rule never went into effect. 83 Fed. Reg. 2,092 (Jan. 16, 2018); 83 Fed. Reg. 11,639 (Mar. 16, 2018). FDA acknowledged the final rule would have changed its "longstanding practices" and explained it was "reverting to the agency's existing and longstanding regulations and interpretations on determining intended use for medical products." Statement from FDA Commissioner Scott Gottlieb, M.D., on FDA Decision to Seek Additional Time to Reassess Rule That Would Have Changed Longstanding Practices for How the Agency Determined the "Intended Use" of Medical Products (Jan. 12, 2018),

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm592358.htm.

FDA issued a new proposed rule in 2020, which deleted the "totality of the evidence" standard, and stated that an "intended use" could not be "based solely on [the manufacturer's] knowledge that such device was being prescribed or used" for a particular use. 85 Fed. Reg. 59,718 (Sept. 23, 2020). However, the proposed rule remained highly ambiguous as to what factors other than a manufacturer's promotional claims would be deemed to create an "intended use," and—in particular—how knowledge might contribute to an "intended use." Additionally, FDA again asserted that its "longstanding position" is that "intended use" can be evaluated based on "any relevant source of evidence." *Id.* at 59,721. The reiteration of this "longstanding position" statement is particularly confusing in light of FDA's acknowledgement in 2018 that the 2017 final rule would have changed FDA's "longstanding practices" for determining "intended use." MIWG submitted comments explaining that the proposed rule continued to exceed FDA's statutory authority and raise constitutional issues. FDA has yet to issue a new final rule.

These developments underscore that the rules governing the communication of off-label information are unclear; FDA itself is wrestling with the meaning of "intended use" and is unable to reach a conclusion; and manufacturers and their employees continue to operate in an intolerably uncertain legal environment. Until clear, binding regulatory guidance is provided, manufacturers cannot know whether a communication or action will be deemed unlawful. The vague, ill-defined standards for determining "intended use" raise significant constitutional concerns, including by chilling manufacturers' communication of truthful, non-misleading information about medical products.

B. "Safe Harbors" For Certain Types Of Off-Label Communications Offer Neither Clarity Nor Precision.

The district court erroneously concluded that the current regulatory regime does not chill the communication of truthful, non-misleading medical information because "FDA guidance" permits such speech in certain circumstances. 2020 WL 5517573, at *14 n.133; *see* FDA, *Revised Draft Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses–Recommended Practices* (Feb. 2014) ("Revised Draft Guidance"); FDA, *Draft Guidance for Industry: Responding to Unsolicited*

Requests for Off-Label Information About Prescription Drugs and Medical Devices (Dec. 2011); FDA, *Guidance for Industry: Good Reprint Practices for 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); FDA, *Guidance for Industry: Industry-Supported Scientific and Educational Activities*, 62 Fed. Reg. 64,093 (Dec. 3, 1997). FDA has stated that it "does not intend" to use certain communications, as described in these guidance documents, as evidence of intended use in an enforcement action against the manufacturer. *E.g.*, Revised Draft Guidance at 6.

The court's reliance on such FDA "safe harbors" is misplaced because they fail to address many types of truthful, non-misleading off-label communications, and therefore do not solve the constitutional issues raised by the vague "intended use" rule. In addition, the guidance documents themselves, which are expressly non-binding and in most cases issued only in draft form, raise First and Fifth Amendment concerns. *Fox Television*, 567 U.S. at 253. Rather than provide fair notice of what is prohibited, these guidance documents often raise new ambiguities for industry to decipher. For example, in 2011, FDA issued a draft guidance on manufacturer

responses to unsolicited requests for off-label information, which introduced a new definition of "solicited" and a distinction between "public" and "non-public" responses untethered to any statutory or regulatory provision. MIWG and other stakeholders submitted comments requesting that FDA clarify its approach. Yet 10 years later, FDA has never revised or finalized the draft.

Moreover, the guidance and regulations that FDA has issued to date fail to cover some of the most significant regulatory issues where there is a lack of clarity, such as the meaning and scope of "scientific exchange" as applied to devices. FDA recognizes "scientific exchange" as a safe harbor for communicating information regarding off-label uses about drugs. *See* 21 C.F.R. § 312.7 (stating FDA's intent "not ... to restrict the full exchange of scientific information concerning" investigational new drugs). No analogous regulation on "scientific exchange" exists for devices, despite MIWG requests that FDA address this issue. While failing to amend its regulations, FDA has long stated that it views the scientific exchange safe harbor as also applying to devices. *See, e.g.*, 42 Fed. Reg. 58,874 (Nov. 11, 1977); 42 Fed. Reg. 49,612 (Sept. 27, 1977); 76 Fed. Reg. 81,508, 81,509 (Dec. 28, 2011).

Even for drugs, FDA has never clarified the precise scope and meaning of "scientific exchange," nor has the agency confirmed that scientific exchange communications are not relevant to determining "intended use." In 2011, in response to MIWG's first petition, the agency requested comments on "all aspects of scientific exchange communications and activities related to off-label uses" of drugs and devices, *see* 76 Fed. Reg. at 81,509, but never took further action despite repeated requests from MIWG and despite FDA's own commitment in 2014 to issuing guidance on scientific exchange. *See* June 6 FDA Letter.

The practice of regulating these important matters through non-binding guidance documents that only address a limited set of manufacturer communications issues raises significant constitutional concerns and impedes the public health by deterring manufacturers from communicating valuable information to health care professionals, payors, and other stakeholders.

III. AS APPLIED IN THIS CASE, THE "INTENDED USE" SPEECH RESTRICTIONS ARE NEITHER CLEAR NOR PRECISE, AND THEREFORE DO NOT COMPORT WITH DUE PROCESS.

A. The District Court's Approach To Determining "Intended Use" Lacks Clarity.

The approach to "intended use" that the district court adopted in this case fails to differentiate clearly between permissible and impermissible speech and conduct, and is therefore fraught with the serious constitutional problems described above. The court concluded that "intended use" can be determined under 21 C.F.R. § 801.4 based on "all relevant sources," without "any limitations on the concept." *Facteau*, 2020 WL 5517573, at *16. These sources include determining "intended use" from internal company documents, even in the absence of any external manufacturer claims promoting the product for that use. *See id.* at *15. That amounts to allowing the jury to find a new "intended use" based on the company's knowledge, as reflected in internal documents, rather than how it marketed the product.

This approach fails to provide the necessary clarity, and instead would give the government virtually limitless discretion. It would also stifle innovation, by threatening manufacturers with crushing penalties for exploring potential beneficial new uses of a product, even if they made no

external claims about the new uses. This approach raises serious constitutional problems and should not be adopted. *See Peaje Invs. LLC v. Garcia-Padilla*, 845 F.3d 505, 511 (1st Cir. 2017) (under "'cardinal principle' of constitutional avoidance," court should not adopt interpretation of statute that raises serious constitutional issues when another interpretation "is fairly possible").

Multiple courts have adopted a different approach, holding correctly that, under the FDCA statutory scheme, "intended use" should be determined by a manufacturer's "specific marketing representations." *Am. Health Prods. Co. v. Hayes*, 574 F. Supp. 1498, 1505 (S.D.N.Y. 1983), *aff'd*, 744 F.2d 912 (2d Cir. 1984). At a minimum, this line of cases highlights the ambiguity in the term. In *Action on Smoking & Health v. Harris*, a citizen petition asked FDA to rely on "consumer intent" to find that cigarettes were drugs under the FDCA, despite the lack of any promotional claims by the manufacturer that cigarettes had therapeutic uses. 655 F.2d 236, 239 (D.C. Cir. 1980). The D.C. Circuit (as well as the FDA) rejected this position, holding that the statutory intent was that "jurisdictional analysis [under the FDCA] would focus upon the existence of *representations made by the manufacturer*." *Id.* at 238 (emphasis added); *see* S. Rep. No. 361, 74th Cong.

1st Sess., 4 (1935) ("The manufacturer of the article, through his representations in connection with its sale, can determine the use to which the article is to be put."). The court further noted that the actual use of a product would support "no inference at all" regarding its intended use, "if such [product] were shipped without advertising" that promotes that use. 655 F.2d at 238.

Similarly, the Eighth Circuit has held that intended use is based on claims that are "promotional in nature" and "distributed in relation to the ... products." *United States v. Articles of Drug for Veterinary Use*, 50 F.3d 497, 501 (8th Cir. 1995). On this basis, the court held that the manufacturer's written material stored in a warehouse could *not* establish intended use, absent a showing that similar claims had been made in marketing the product. *Id.*; *see United States v. One Unlabeled Unit, More or Less, of an Article of Device and Promotional Brochures*, 885 F. Supp. 1025, 1028 (N.D. Ohio 1995) (intended uses "must be determined from objective evidence in promoting, distributing and selling the device"). And "even the FDA has repeatedly stated that it may only regulate claimed uses of drugs, not all foreseeable or actual uses." *Ass'n of Am. Physicians & Surgeons, Inc. v. FDA*, 226 F. Supp. 2d 204, 217-18 (D.D.C. 2002) (FDA exceeded statutory authority in seeking to

regulate uses of drugs not claimed by manufacturers); *see, e.g.*, Defs.' Reply in Supp. of Mot. to Dismiss and for Summ. J. at 6, *Allergan v. United States*, No. 09-cv-01879 (D.D.C. Mar. 29, 2010), ECF No. 37 ("Statements regarding unapproved uses that do *not* 'prescribe,' 'recommend,' or 'suggest' that the drug be put to those uses are not promotional and do not trigger" intended use provisions).

This Court's precedents are in accord, though the district court misinterpreted them. It held that *V.E. Irons, Inc. v. United States*, 244 F.2d 34 (1st Cir. 1957), rejected a claims-based interpretation of intended use because it states that courts can "look to 'all relevant sources.'" 2020 WL 5517573, at *16. The district court concluded that, while this Court "did not explicitly delineate what materials it intended to bring within the scope of 'all relevant sources,' it did not articulate any limitations on the concept," nor "did it say that internal communications could not be reviewed." *Id.*

This expansive interpretation misreads *V.E. Irons*. In context, "all relevant sources" refers to all relevant sources *of promotional claims*. The Court rejected an argument that the intended use analysis should be confined "to the labels on the drug or the 'labeling,'" holding that it encompasses promotional materials as well. 244 F.2d at 44. And every source

the Court mentions—"all of appellants' literature as well as the oral representations made ... at [appellants'] lectures or by authorized sales distributors"—is promotional. *Id*. *V.E. Irons* does not hold or even suggest that the Court could find an intended use never mentioned in the manufacturer's claims about its products. *Id*. Similarly, *Nature Food Ctrs., Inc. v. United States*, 310 F.2d 67, 69-70 (1st Cir. 1962), determined "intended use" based on promotional "lectures" and "notes" distributed by company representatives that "made fulsome claims as to the preventative and curative qualities of [the] various products."

At a minimum, if the government has a different view of intended use and believes that intended use can be determined in the absence of promotional claims, it had an obligation to articulate clearly and precisely what factors it believed give rise to criminal liability prior to when the defendants engaged in the conduct at issue. But FDA has never articulated clear rules for determining how factors *other than* promotional claims create a new intended use upon which criminal culpability can be predicated.[6]

[6] MIWG has advocated for confirmation from FDA of a claims-based interpretation of intended use, including in response to FDA's 2020 proposed rule. *See, e.g.*, Comments on Regulations Regarding "Intended

B. The Lack Of Clarity Regarding "Intended Use" Undermines Defendants' Convictions.

The district court below acknowledged the serious implications of the lack of clarity in the current regulatory framework by stating bluntly that the "statutory and regulatory scheme needs to be rethought." *Facteau*, 2020 WL 5517573, at *1. Recognizing how "important" it is "for the regulatory and law enforcement regime to clearly spell out what is and is not prohibited conduct," the district court explained that "off-label marketing" prosecutions "*criminaliz[e] conduct that it is not entirely clear Congress intended to criminalize*." *Id.* (emphasis added).

Following its own logic, the court should have recognized that the vagueness issues here make criminal sanctions impermissible. The Defendants' convictions based on the unclear regulatory framework raise precisely the due process and vagueness issues discussed above. After decades of ambiguous and often contradictory statements from the government as to the scope of permissible communications and the evidence that will establish an "intended use," employees of manufacturers cannot

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Uses," Docket No. FDA-2015-N-2002 (Oct. 23, 2020), *available at* www.miwg.org.

reasonably be expected to "know what [was] required of them so they [could] act accordingly." *Fox Television*, 567 U.S. at 253.

Those problems are compounded here because the jury was instructed that it could convict the Defendants of FDCA misdemeanors even if they lacked any intent to cause the introduction of adulterated or misbranded devices, Jury Instructions at 19-20, No. 1:15-cr-10076 (D. Mass. July 15, 2016), ECF No. 434, and indeed the jury found that the Defendants did *not* intend to defraud or mislead, Verdict Form at 4-19, No. 1:15-cr-10076 (D. Mass. July 15, 2016), ECF No. 432. A "scienter requirement may mitigate" due process problems caused by an unclear law, "especially with respect to the adequacy of notice to the complainant that his conduct is proscribed." *Vill. of Hoffman Estates v. Flipside, Hoffman Estates, Inc.*, 455 U.S. 489, 499 (1982). But in this case, there was no scienter requirement or finding that could "mitigate [the] law's vagueness." *Id.* In these circumstances, neither Defendant could reasonably be expected to "conform his conduct" to the law. *See Project B.A.S.I.C.*, 947 F.2d at 21.

The ambiguous regulatory regime and the due process concerns implicated by the Defendants' convictions are also exemplified by other parts of the jury instructions. The instructions did not provide the jury with

clear standards of what was permissible to consider in determining whether a new intended use had been established. The instructions stated that "'intended use' refers to the objective intent of the manufacturer" and that such intent "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." Jury Instructions at 10-11, ECF No. 434. The instructions added 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." *Id.* at 11. However, the instructions did not elaborate upon what "mere knowledge" means, or whether and how "knowledge" could be relevant in conjunction with other factors. This lack of clarity in the instructions is likely because the government has never clarified these issues, either in this case or more generally.

Nor did the instructions explain how the jury should evaluate "intended use" in a scenario where a manufacturer has knowledge of an off-label use and has also engaged in speech under an FDA "safe harbor," such as manufacturer responses to unsolicited requests for information regarding off-label uses. Knowledge in combination with such "safe-

harbored" speech should not create a new intended use, as FDA itself has stated. *See, e.g.*, 85 Fed. Reg. at 59,725).

Different juries, even if they agreed on the underlying facts, could have reached different conclusions, based on the instructions provided, regarding whether defendants' knowledge in combination with other circumstances (including "safe-harbored" speech) gave rise to a new "intended use." That lack of clarity as to whether a particular set of facts constitutes criminal conduct is the direct result of ambiguity in the regulatory regime. If FDA and industry stakeholders cannot articulate the correct legal standard for a new intended use and the appropriate role of evidence that may be considered as part of the "intended use" inquiry (*see* Section II, *supra*), it should come as no surprise that a jury of laypersons would have difficulty applying the same ambiguous standards, making it impossible to know in advance when one has crossed the line into impermissible conduct. As previously noted, such ambiguity is particularly concerning in the criminal context. *See, e.g.*, *Buckley*, 424 U.S. at 76-77.

A jury verdict cannot stand if it is based upon—or may plausibly have been based upon—an interpretation of regulatory requirements that have not been adequately defined in accordance with constitutional dictates. *See*

United States v. Prigmore, 243 F.3d 1, 18, 24 (1st Cir. 2001) (vacating Defendants' convictions related to failing to seek FDA approval of a supplemental application after modifying their medical device because there was "too great a possibility that the jury's verdicts were affected by an erroneous failure to define crucial and disputed regulatory terms"); *Cf. United States v. Anzalone*, 766 F.2d 676, 678, 682–83 (1st Cir. 1985) (reversing a defendant's conviction on vagueness grounds because federal regulations as "presently read" failed to "forewarn of the proscription of said conduct" and noting that the "Constitution ... mandates that, before any person is held responsible for violation of the criminal laws of this country, the conduct for which he is held accountable be prohibited with sufficient specificity to forewarn of the proscription of said conduct"); *Grayned v. City of Rockford*, 408 U.S. 104, 113-14 (1972) ("define[d] boundaries" must be "sufficiently distinct for ... juries" for laws to satisfy fair warning requirements (internal quotation marks omitted)).

Just as in *Prigmore*, where the jury instructions failed to define clearly the requirement for filing a supplement and therefore "might well have left the jury with an erroneous belief that manufacturers face criminal liability" based on the government's "overly broad" interpretation of the requirement,

243 F.3d at 20-21, the jury instructions in this case failed to provide clear standards of what was permissible to consider in determining "intended use." Consequently, the Defendants might well have been convicted based on the jury's erroneous understanding of "intended use." *Cf. McDonnell*, 136 S. Ct. at 2375 (vacating conviction "because the jury was not correctly instructed on the meaning of" a disputed statutory term and "may have convicted [the defendant] for conduct that is not unlawful"). Defendants' convictions based on unclear jury instructions also threaten to exacerbate the chill on truthful, non-misleading manufacturer communications—including scientific exchange valuable to the public health—resulting from the lack of clear rules to enable manufacturers to determine in advance whether their communications are lawful.

CONCLUSION

For the foregoing reasons, the Court should reverse the judgment of the district court.

Date: July 28, 2021

Respectfully Submitted,

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