UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

UNITED STATES OF AMERICA **v.** **WILLIAM FACTEAU,** **and** **PATRICK FABIAN,** **Defendants.**	**Crim. No. 15-10076-ADB**

BRIEF OF *AMICI CURIAE* MEMBERS OF THE MEDICAL INFORMATION WORKING GROUP IN SUPPORT OF DEFENDANTS' MOTION FOR A JUDGMENT OF ACQUITTAL OR, ALTERNATIVELY, A NEW TRIAL

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RULE 7.1 CORPORATE DISCLOSURE STATEMENT

Pursuant to Federal Rule of Civil Procedure 7.1, and to enable District Judges and Magistrate Judges of the Court to evaluate possible disqualification or recusal, 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*: Allergan plc, Amgen Inc., Bayer Healthcare Pharmaceuticals, Inc., Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb, Eli Lilly and Company, Genentech, Inc., GlaxoSmithKline LLC, Novartis Pharmaceuticals Corporation, Novo Nordisk, Inc., Pfizer Inc., and sanofi-aventis U.S. LLC.

The undersigned counsel for *amici curiae* certifies further that the following are corporate parents, affiliates and/or subsidiaries of such members, which are publicly held:

- Allergan plc is a corporation with publicly traded stock of which no publicly traded corporation owns more than 10%.
- Amgen Inc. is a corporation with publicly traded stock of which no publicly traded corporation owns more than 10%.
- Bayer Healthcare Pharmaceuticals Inc. is a subsidiary of Schering Berlin Inc., both of which, through a series of intermediaries, are subsidiaries of Bayer AG, a corporation whose stock is publicly traded in Germany. Bayer AG has no parent company and no publicly held company which owns 10% or more of its stock.
- 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.
- Eli Lilly and Company is a corporation with publicly traded stock of which no publicly traded corporation owns more than 10%.
- Genentech Inc. is a wholly owned subsidiary of Roche Holdings, Inc., whose ultimate parent is Roche Holding Ltd. Roche Holding Ltd. has no parent corporation and is pub-

licly traded on the Swiss Stock Exchange. On information and belief, Novartis AG holds either directly or indirectly more than 10% of the voting shares of Roche Holding Ltd.

- 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 AGs, 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.

- Novo Nordisk A/S is a corporation with publicly traded stock of which no publicly traded corporation owns more than 10%.

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

- sanofi-aventis U.S. LLC is a wholly-owned subsidiary of sanofi S.A., a corporation with publicly traded stock of which no publicly traded corporation owns more than 10%.

STATEMENT OF INTEREST

Members of the Medical Information Working Group (MIWG) respectfully submit this *amici curiae* brief to assist the Court in resolving important constitutional issues pertinent to the Defendants' motion for a judgment of acquittal or a new trial.[1]

The MIWG is an informal working group of major manufacturers of biopharmaceutical products and medical devices. The MIWG was formed in 2006 to improve the federal regulatory framework and enforcement climate affecting manufacturer dissemination of information about their products, including information about unapproved products and new uses of approved products. The MIWG and its members have made numerous submissions to the Food and Drug Administration (FDA), including two Citizen Petitions (in 2011 and 2013). These submissions have requested clarification of, and substantive changes to, the existing regulatory framework. An Appendix to this brief presents a complete timeline of these efforts.

In particular, the MIWG has sought to address concerns that the current enforcement scheme is at odds with fundamental First and Fifth Amendment principles that permit manufacturers to engage in truthful and non-misleading communications about off-label uses of their products. The unclear rules that characterize the regulatory framework, and the Government's expansive and ad-hoc approach to enforcement, provide inadequate notice of the line between permissible and impermissible speech and, as a result, manufacturers' constitutionally protected speech is chilled. The risk of improperly chilling protected speech has become even more pronounced given the Department of Justice's enhanced efforts to investigate and prosecute individ-

[1] The members of the MIWG include: Allergan plc, Amgen Inc., Bayer Healthcare Pharmaceuticals Inc., Boehringer Ingelheim Pharmaceuticals, Inc., Bristol Myers Squibb Company, Eli Lilly and Company, Genentech, Inc., Johnson & Johnson, GlaxoSmithKline LLC, Novartis Pharmaceuticals Corporation, Novo Nordisk A/S, Pfizer Inc., and sanofi-aventis U.S. LLC. Johnson & Johnson is a member of the MIWG, but neither Johnson & Johnson nor its counsel has authored, in whole or in part, or made a monetary contribution intended to fund the preparation or submission of this brief.

uals for alleged corporate wrongdoing, a strategy directly at issue in this case. *See* Mem. of S. Yates, Deputy Attorney General, *Individual Accountability for Corporate Wrongdoing* 1-2 (Sept. 9, 2015), *available at* http://www.justice.gov/dag/file/769036/download.

In addition, the MIWG has participated as *amicus curiae* in leading cases addressing constitutional protection for truthful, non-misleading speech about FDA-approved products. *See United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012); *Amarin Pharm., Inc. v. FDA*, 119 F. Supp. 3d 196 (S.D.N.Y. 2015); *Pacira Pharm., Inc. v. FDA*, No. 15-cv-07055 (S.D.N.Y. 2015) (favorably resolved). Accordingly, the MIWG's members bring an important perspective to bear on issues central to this case.

INTRODUCTION AND SUMMARY

In acquitting the Defendants of wire fraud, conspiracy, intent to defraud or mislead, and false or misleading labeling, the jury soundly rejected the government's view that this case is about fraud. As it now stands, this case implicates three significant constitutional issues that arise frequently in Federal Food, Drug, and Cosmetic Act (FDCA) prosecutions involving off-label speech.

First, the regulatory regime surrounding drug and device manufacturers' speech about lawful uses of their products—whether on- or off- label—is extremely ambiguous. In particular, FDA's long-standing failure to clarify what creates a new "intended use" (and thus can give rise to a misbranding prosecution) leaves manufacturers without clear guidance about the extent to which FDA believes they can lawfully discuss, or even consider internally, different uses for their products. *Infra* pp. 5-9. This lack of guidance has persisted for decades, despite repeated attempts by industry, and ten years of coordinated efforts by the MIWG in particular, to obtain clarity. *Infra* pp. 9-11. This persistent ambiguity about what speech will create criminal liability contravenes the fundamental due process and free speech principles that the government must

"give fair notice of conduct that is forbidden or required." *FCC v. Fox Television Stations, Inc.*, 132 S. Ct. 2307, 2317 (2012); *see infra* pp. 11-12.

Second, these due process problems are exacerbated by the FDCA's imposition of strict criminal liability. Where, as here, the governing law is unclear, a "scienter requirement may mitigate" the due process problems caused by the law's vagueness. *Village of Hoffman Estates v. Flipside, Hoffman Estates, Inc.*, 455 U.S. 489, 499 (1982). But there is no such requirement here: a defendant can be held liable for an FDCA misdemeanor—which carries a year-long jail sentence, *see* 21 U.S.C. § 333(a)(1)—notwithstanding the absence of any criminal intent. In that situation, it is nearly impossible for even the most conscientious employee of a manufacturer to ensure that her conduct does not run afoul of the law—or the government's after-the-fact interpretation of the law. *Infra* pp. 11-13.

Third, truthful, non-misleading speech about lawful uses of drugs or devices—including off-label uses, which are both legal and therapeutically valuable—is fully protected by the Constitution. This speech provides valuable information to the medical community and drives innovation. Accordingly, even if the government provides notice sufficient to satisfy due process, constitutional principles bar it from "criminalizing the truthful off-label promotion of FDA-approved prescription drugs." *United States v. Caronia*, 703 F.3d 149, 168 (2d Cir. 2012). This Court has recognized this principle. *See* Jury Instructions at 26 (ECF No. 436) ("The FDCA does not prohibit or criminalize truthful, not misleading off-label promotion."). *Infra* pp. 13-18.

Here, the Defendants' FDCA convictions implicate all three of these principles. First, under the current, ambiguous regulatory regime, a conviction based on allegations that off-label promotion created a new "intended use" necessarily implicates the due process notice issues described above, for there is no clear rule defining what "uses" and types of communication will

trigger a new "intended use." As a result, a corporate official in the Defendants' position could not know in advance whether and to what extent truthful, non-misleading communications about new uses are permitted or prohibited. *Infra* p. 11-12.

Second, those due process problems are amplified here by the absence of any *mens rea* requirement. The jury was told that it could convict the Defendants of causing FDCA violations even if they did not intend any wrongdoing. Jury Instructions at 30-42. On that basis, the jury could have convicted the Defendants simply for failing to abide by unclear rules in the absence of any evidence that the Defendants intended to do anything wrong. *Infra* pp. 11-12.

Third, the jury's rejection of the government's fraud theory leaves the defendants' convictions resting on truthful, non-misleading speech about lawful uses of their company's device. As the Supreme Court has held and this Court has recognized, such speech cannot, consistent with the First Amendment, form the basis for a criminal conviction. *See Sorrell v. IMS Health Inc*., 564 U.S. 552, 557 (2011) ("Speech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment."); Jury Instructions at 32 ("The FDCA does not prohibit or criminalize truthful, not misleading off-label promotion."). The government argues that truthful, non-misleading speech may be used as "evidence" of intended use, but such speech may properly be used to establish intent only where there is a separate *actus reus*. Where there is no such independent *actus reus*—and there would be no crime but for the truthful, non-misleading off-label speech—a proper *actus reus* does not exist to support a criminal conviction. Moreover, consistent with fundamental Fifth Amendment principles, any alleged independent *actus reus* would need to be defined clearly to ensure that the jury understood the alleged misconduct and the evidence upon which it could rely in rendering its verdict. That standard was not satisfied here. Accordingly, any effort by the government now to

assert an independent *actus reus* in support of the defendants' convictions would fail to meet basic due process requisites. *Infra* pp. 17-18.

ARGUMENT

I. THE RULES GOVERNING MANUFACTURER SPEECH REMAIN VAGUE NOTWITHSTANDING INDUSTRY'S SUSTAINED EFFORTS TO SEEK NEEDED CLARITY.

FDA's approach to regulating medical device products fails to inform regulated parties what they can and cannot say about off-label uses of their products—notwithstanding the industry's extensive efforts over the last decade to obtain clarity in the regulatory regime. This absence of clear standards is significant in cases, like this one, where the government criminally prosecutes manufacturers or their employees for speech regarding their products.

A. The Existing Regulatory Regime Surrounding Manufacturer Communications About Medical Products Does Not Draw Clear Lines Between Permissible And Impermissible Speech.

The FDCA does not prohibit "off-label promotion" as such. Instead, as in this case, most violations of the FDCA that are premised on a manufacturer's product-related speech are framed as "misbranding," "adulteration," or both. The government argues that a manufacturer's off-label communication causes a medical device to be misbranded under section 502(o) of the FDCA, 21 U.S.C. § 352(o), because it triggers the requirement to obtain further clearance under section 510(k) of the FDCA, 21 U.S.C. § 360(k).[2] Likewise, the government argues that a device is adulterated under section 501(f)(1)(B), 21 U.S.C. § 351(f)(1)(B), if it is promoted for a new intended use that triggers the requirement to obtain premarket approval but lacks such approval.

[2]The government has also argued that a device is misbranded under section 502(f)(1), 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 the government's argument that the device had inadequate directions for use.

Prosecution under these theories often depends on the government's characterization of a manufacturer's "intended uses," a term defined in FDA's regulations 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" 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. And although courts have repeatedly "read . . . 'intended' to refer to specific marketing representations," *Am. Health Prods. Co. v. Hayes*, 574 F. Supp. 1498, 1505 (S.D.N.Y. 1983), the current enforcement scheme gives manufacturers little notice as to what external communications will cause the government to conclude that a new intended use has been created.

Further, FDA has never articulated clear rules for determining whether information *other than* external communications—such as internal documents that make no claims to potential users—can create a new intended use upon which criminal culpability can be predicated. Indeed, use of such internal documents to determine a device's "intended use" is contrary to the plain language of FDA's own regulation, which requires evidence of "objective intent." *See* 21 C.F.R. § 801.4; *cf. Ass'n of Am. Physicians & Surgeons*, 226 F. Supp. 2d 204, 217-18 (D.D.C. 2002) (noting that "even the FDA has repeatedly stated that it may only regulate claimed uses of drugs, not all foreseeable or actual uses"); *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"). Basing liability on internal documents would also stifle the very innovation that

leads to beneficial new devices and uses. Regardless, if FDA has a different view, it must articulate clearly what facts it believes can give rise to criminal liability. It has not done so.

These problems are long-standing. Over two decades ago, regulated parties attempted to spur FDA to promulgate clear, constitutionally appropriate rules through citizen petitions, *see* 59 Fed. Reg. 59,820, 59,821 (Nov. 18, 1994), and litigation, *see Wash. Legal Found. v. Kessler*, 880 F. 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, *see* 67 Fed. Reg. 34,942 (May 16, 2002), but did not clarify the regulatory framework. More recently, in 2011, the agency requested comments on "all aspects of scientific exchange and activities related to off-label uses" of drugs and devices, *see* 76 Fed. Reg. 81,508, 81,509 (Dec. 28, 2011), but once again, did not clarify the regime. The same week, the agency released draft guidance on unsolicited requests; that draft still has not been finalized. 76 Fed. Reg. 82,303 (Dec. 30, 2011).

The government has used this regulatory ambiguity against the Defendants here. Despite repeated assurances that "knowledge" of off-label use does not render an approved product misbranded, the government pursued just such a theory of criminal liability, on a strict-liability basis, in this case. The Department of Justice has repeatedly told federal courts that, despite the language of 21 C.F.R. § 801.4, "knowledge" of a product's off-label use is not a basis for finding that the use is an "intended use."[3] Only in September 2015, however, did FDA finally issue a

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

proposed rule to amend the intended use regulations to conform to those representations. *See* 80 Fed. Reg. 57,756 (Sept. 25, 2015). This proposed rule eliminates text from the regulations that could be construed as imputing a new intended use for a drug or device based only on a manufacturer's knowledge of that use—rather than its claims about the product.

Yet, as an example of the unconstitutional ambiguity in the enforcement regime, the government has in this case relied on the very language that it has not only proposed to delete, but also acknowledged does not accurately reflect FDA's policy. *See* Opp'n to Defs.' Mot. for Production of Legal Instructions to Grand Jury at 13-14 (ECF No. 101) (asserting that "[d]efendants are mistaken" in their argument that "a manufacturer's knowledge that its device will be used for an unapproved use is wholly irrelevant to the manufacturer's legal obligations," stating that "the regulation describing intended use is clear on this topic," and quoting the specific text that the proposed rule would delete).[4]

It is under this web of vague regulations, unclear and shifting "draft" sub-regulatory guidance—which is not, in any event, binding—and ad hoc government enforcement actions that manufacturers must currently operate.

[4] Though FDA purports to exempt certain types of communication from its regulatory ban, these "safe harbors" offer neither clarity nor precision. A single regulation states the agency's intent "not . . . to restrict the full exchange of scientific information concerning" investigational new drugs, 21 C.F.R. § 312.7, and there is no such rule for devices. Otherwise, manufacturers are left to divine what information may lawfully be shared from non-binding and vague guidance documents—which frequently change without warning. *E.g.*, Revised Draft Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses – Recommended Practices (Feb. 2014); Draft Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices (Dec. 2011); Guidance for Industry: Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64,093 (Dec. 3, 1997). Nor can manufacturers count on securing clarification directly from FDA, which has indicated that it "no longer issue[s] advisory opinions." Letter from Susan H. Hargrove, Smith, Anderson, Blount, Dorsett, Mitchell & Jernigan LLP to Jane A. Axelrad, Assoc. Dir for Policy, CDER (Sept. 9, 2009).

B. MIWG Has Tried Unsuccessfully To Obtain Clarity From FDA About The Scope Of Permissible Communications For Nearly A Decade.

The MIWG has repeatedly requested that FDA make substantive changes to—or at least clarify—the regulatory framework for communicating off-label information. In addition to numerous written submissions dating back nearly ten years, the MIWG has held meetings dating back to 2007 with senior FDA officials including the FDA Chief Counsel, the Associate Commissioner for Policy, and the Commissioner.[5]

Most pertinent to this litigation, the MIWG has filed two Citizen Petitions requesting specific actions and clarifications. In 2011, MIWG's first petition asked that FDA address manufacturer responses to unsolicited requests, scientific exchange, payor communications, and dissemination of third-party clinical practice guidelines; a 2013 petition renewed those concerns and also requested that, in view of intervening case law developments, FDA comprehensively review and modify its regulatory framework in view of constitutional and statutory limitations. On June 6, 2014, FDA granted those petitions. The agency said at the time 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 the calendar year." Letter from Leslie Kux, Assistant Commissioner for Policy, FDA to Alan R. Bennett and Joan McPhee, Ropes & Gray LLP, and Coleen Klasmeier and Paul Kalb, Sidley Austin LLP, Docket Nos. FDA-2011-P-0512 and FDA-2013-P-1079 (June 6, 2014). On December 22, 2014, by which time it was obviously going to miss the deadline, the agency extended that timeline, stating in a letter to the MIWG that "[o]ur current goal is to issue guidance that addresses manufacturer dissemination of information regarding unapproved uses during

[5] A complete timeline of the MIWG's efforts to obtain clarity is attached hereto as an Appendix.

the first part of 2015." Letter from Leslie Kux, Assistant Commissioner for Policy, FDA to Alan R. Bennett and Joan McPhee, Ropes & Gray LLP, and Coleen Klasmeier and Paul Kalb, Sidley Austin LLP, Docket Nos. FDA-2011-P-0512 and FDA-2013-P-1079 (Dec. 22, 2014). FDA has met none of these self-imposed deadlines.

Just recently, the agency announced its intention to hold a two-day public hearing on November 9-10, 2016, and has solicited associated public comments, to address its "regulations and policies governing firms' communications about unapproved uses of approved/cleared medical products," noting that it is "engaged in a comprehensive review" of those regulations and policies. 81 Fed. Reg. 60,299, 60,300 (Sept. 1, 2016). FDA is accepting comments until January 9, 2017, *id.* at 60,299, meaning that any action by the agency remains many months away—at best. For that matter, the agency has given no signal that it plans to address the foundational constitutional deficiencies in the regulatory scheme. *See, e.g.*, James M. Beck, *More Talk – No Action – From FDA on Off-Label "Communication,"* DRUG & DEVICE LAW (Sept. 6, 2016) (noting that "the term 'First Amendment' doesn't appear anywhere" in FDA's notice and observing that FDA still "refuses to recognize[] the constitutional bind in which it finds itself"), *available at* http://goo.gl/NGcZgJ. And even if FDA does attempt to address these issues, the fundamental First Amendment limits on its ability to criminalize truthful speech will remain. *See infra* pp. 13-18.

These developments underscore that FDA's rules governing the communication of off-label information are unclear; that the agency itself is wrestling with their meaning and is unable to reach a conclusion; and that manufacturers and their employees are currently operating in an intolerably uncertain legal environment. Until clear and binding regulatory guidance is provided,

manufacturers cannot know whether a specific truthful, non-misleading communication or action will be deemed unlawful.

C. The First Amendment And The Due Process Clause Require Speech Restrictions To Be Clear And Precise.

This persistent lack of regulatory clarity presents a serious due process problem. "[O]ne of the most basic" standards of our "system of justice" 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) (quoting *NAACP v. Button*, 371 U.S. 415, 433 (1963)). 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." *FCC v. Fox Television Stations, Inc.*, 132 S. Ct. 2307, 2317 (2012). And "[w]hen speech is involved, rigorous adherence to those requirements is necessary to ensure that ambiguity does not chill protected speech." *Id.*; *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"). As the discussion above makes clear, FDA's current regulatory framework lacks the clarity and specificity required by due process.

II. THE DUE PROCESS CONCERNS PRESENTED BY THE UNCLEAR REGULATORY FRAMEWORK ARE COMPOUNDED BY THE FDCA'S IMPOSITION OF STRICT CRIMINAL LIABILITY.

The vagueness problems discussed above are exacerbated by the FDCA's imposition of criminal liability in the absence of intent. Where the law is unclear—as it undisputedly is here,

see supra pp. 5-10—a "scienter requirement may mitigate [the] law's vagueness, especially with respect to the adequacy of notice to the complainant that his conduct is proscribed." *Village of Hoffman Estates v. Flipside, Hoffman Estates, Inc.*, 455 U.S. 489, 499 (1982); *see also United States v. Ford*, 821 F.3d 63, 70 (1st Cir. 2016) (unawareness of the law typically is not a defense, except where "the defendant has 'such insufficient notice [of the law] that it [falls] outside the bounds of due process'" (alterations in original)); 1 WAYNE R. LAFAVE & AUSTIN W. SCOTT, JR., SUBSTANTIVE CRIMINAL LAW § 2.3, at 130 (2d ed., Oct. 2015 update) (collecting Supreme Court cases holding that an allegedly vague statute "gives fair warning because scienter is an element of the offense"). But the FDCA contains no such requirement for the imposition of misdemeanor liability; rather, it "imposes strict liability misdemeanor punishment for conduct committed without *mens rea*." *In re Grand Jury Subpoena*, 220 F.R.D. 130, 155 (D. Mass. 2004).

Here, the Defendants' convictions raise precisely these due process issues. After decades of unclear and often contradictory guidance from FDA as to the scope of permissible communications and the evidence that will establish an "intended use," employees of manufacturers cannot reasonably be expected to "know what [was] required of them so they [could] act accordingly." *Fox Television*, 132 S. Ct. at 2317. 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 30-40, and indeed the jury found that the Defendants did *not* intend to defraud or mislead, Verdict Form at 4-19 (ECF No. 432). There was therefore no "scienter requirement" or finding that could "mitigate [the] law's vagueness." *Hoffman Estates*, 455 U.S. at 499. 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.

III. TRUTHFUL, NON-MISLEADING SPEECH ABOUT LAWFUL USES OF MEDICAL PRODUCTS IS CONSTITUTIONALLY PROTECTED AND CANNOT FORM THE BASIS FOR A CRIMINAL CONVICTION.

The lack of clear standards in this area is of particular constitutional concern. A manufacturer's truthful, non-misleading speech about the potential lawful uses of its medical devices, whether those uses are on- or off-label, is valuable to doctors and patients alike, and is fully protected by the First Amendment.

The Supreme Court has recognized that "[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). Content- and speaker-based restrictions on such speech therefore face "heightened judicial scrutiny." *Id.* In turn, where a manufacturer speaks truthfully, and in a non-misleading fashion, about how its approved products may be lawfully used, any restriction on that speech—whether it is a ban or merely a burden—must at least "directly advance[] a substantial governmental interest" and be carefully "drawn to achieve that interest." *Id.* at 565-66, 572.

These principles apply fully to off-label speech about lawful uses of FDA-approved or -cleared products. In *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012), the Second Circuit rejected the government's attempt to treat the defendant's truthful and non-misleading promotional claims about approved products as criminal misbranding under the FDCA. *Id.* at 168. The government could not satisfy the heightened scrutiny triggered by the government's content- and speaker-based restrictions: because "off-label drug usage is not unlawful, and the FDA's drug approval process generally contemplates that approved drugs will be used in off-label ways," "prohibiting off-label promotion by a pharmaceutical 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. And the restrictions imposed by the gov-

ernment were "more extensive than necessary" to permit effective regulation of drugs and devices. *Id.* at 167. Consequently, "criminalizing the truthful off-label promotion of FDA-approved prescription drugs" "would unconstitutionally restrict free speech." *Id.* at 168; *see also Amarin Pharm., Inc. v. FDA*, 119 F. Supp. 3d 196, 224 (S.D.N.Y. 2015) (confirming that "the FDA may *not* bring such an action based on truthful promotional speech alone, consistent with the First Amendment"). This Court thus recognized, and instructed the jury, that it "may not convict a Defendant of a crime based solely on truthful, non-misleading statements promoting an FDA-cleared or approved device." Jury Instructions at 26.

There are good reasons for the First Amendment's robust protection of truthful and non-misleading speech about FDA-approved products. "[T]he extension of First Amendment protection to commercial speech is justified principally by the value to consumers of the information such speech provides." *Zauderer v. Office of Disciplinary Counsel of Supreme Court of Ohio*, 471 U.S. 626, 651 (1985). This principle "has great relevance in the fields of medicine and public health, where information can save lives." *Sorrell*, 564 U.S. at 566. Moreover, because "manufacturers have superior access to information about their drugs," *Wyeth v. Levine*, 555 U.S. 555, 578-79 (2009), they are frequently the most well-informed speakers in the informational marketplace. Restricting the speech of manufacturers therefore degrades the quality of information accessible to doctors, patients, scholars, and payors.

A manufacturer's dissemination of information is no less valuable—nor any less protected—when it concerns off-label uses of approved products. "[O]ff-label drug usage is not unlawful." *Caronia*, 703 F.3d at 166. Indeed, "the FDA generally does not regulate how physicians use approved drugs." *Id.* at 153. Recognizing the value of off-label uses of approved products, Congress declined, when passing the FDCA, to "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*." 21 U.S.C. § 396 (emphasis added); *see also* 21 C.F.R. § 312.2(d) (leaving unregulated "the use in the practice of medicine for an unlabeled indication of a new drug product approved" by FDA). This was not an oversight. Off-label use "is an accepted and necessary corollary of the FDA's mission to regulate in this area without directly interfering with the practice of medicine." *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 & n.5 (2001).

Further, "the therapeutic—indeed, sometimes life-saving—value of off-label uses of FDA approved drugs has been widely recognized." *Amarin*, 119 F. Supp. 3d at 201. Because "[t]he full and ultimate role of a drug is rarely evident at the time of its initial approval and labeling," limiting a drug to its approved uses only would drastically and artificially restrict its value. *See* Am. Acad. of Pediatrics, Comm. on Drugs, *Uses of Drugs Not Described in the Package Insert (Off-Label Uses)*, 110 PEDIATRICS 181, 182 (2002). In fact, as FDA itself recognizes, off-label use "may even constitute a medically recognized standard of care" for certain conditions. FDA, Draft Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices 2 (Dec. 2011); *see also* Mem. of the AMA House of Delegates, Resolution 820, *Off-Label Use of Pharmaceuticals* (Sept. 21, 2005) (where it is the standard of care, a physician's failure to prescribe off-label constitutes malpractice), *available at* http://tinyurl.com/yfpwmyo. Indeed, federal law *requires* the government to reimburse Medicare and Medicaid patients for certain off-label treatments. *See* 42 U.S.C. § 1396r-8(k)(6); Medicare Benefit Policy Manual, Ch. 15, § 50.4.2. Finally, in some cases, off-label use may provide not only "the best available intervention for a patient," but also "the only treatment option." Rebecca Dresser & Joel Frader, *Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, 37(3) J. L. MED. & ETHICS 476, 481 (2009). All

of this is true of off-label uses of devices as well. *See Buckman Co.*, 531 U.S. at 350. And it is often manufacturers who possess the most comprehensive and reliable information about such uses of their products, making their speech on this topic especially valuable to medical professionals.

Given these critical public health considerations, "it only furthers the public interest to ensure that decisions about the use of prescription drugs, including off-label usage, are intelligent and well-informed." *Caronia*, 703 F.3d at 167; *see also* 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, 307 (2010) ("[W]here the challenged off-label information is truthful, what is the public interest in forbidding it?"). To restrict a manufacturer's ability to provide valuable, truthful information to those who need it runs counter not only to common sense, but also to the basic First Amendment principle that favors "more speech, not enforced silence." *See, e.g.*, *Linmark Assocs., Inc. v. Twp. of Willingboro*, 431 U.S. 85, 97 (1977).

Nor will faithfully applying the First Amendment's commands in this realm undermine the FDA's broader regulatory regime. As *Caronia* recognized, the FDA could pursue "[n]umerous, less speech-restrictive alternatives" to fulfill its mission of protecting the public health. 703 F.3d at 167. For example, the First Amendment leaves FDA free to engage in counter-speech, including by "guid[ing] physicians and patients in differentiating between misleading and false promotion, exaggerations and embellishments, and truthful or non-misleading information," *id.* at 168; or "develop[ing] its warning or disclaimer systems" to inform health care providers and the public that a particular use has not been approved or cleared by the agency, or that a use may present risks to the patient, *id.* Furthermore, nothing is stopping FDA from im-

plementing other policy changes—like those the MIWG has been proposing for years—to conform its regulatory approach to the First and Fifth Amendments. *See id.*; *supra* pp. 8-9 (describing the MIWG's citizen petitions).

Given the jury's finding that the Defendants neither acted with intent to defraud or mislead, either affirmatively or by omission, nor caused the use of false or misleading labeling, this case squarely implicates these important First Amendment principles. Indeed, "*Caronia* construed the misbranding statute, categorically, not to reach a manufacturer" where the charge "takes aim at truthful, non-misleading speech." *Amarin*, 119 F. Supp. 3d at 228. Put simply, in light of the jury's finding, the speech at issue in this case cannot form the basis for a conviction.

It is no answer to say that the Defendants' (or their employees') truthful, non-misleading speech was used as mere "evidence" of intended use rather than as the actual predicate for conviction. Such speech may be used to establish intent only where there is a "proper *actus reus*." *See id*. That may exist in a misbranding case involving false or misleading promotional speech that is not entitled to First Amendment protection, or in a case that rests on criminal *conduct* as opposed to speech as the *actus reus*. A proper *actus reus* does not exist, however, where there would be no crime but for the truthful, non-misleading off-label speech. And because, as the government has itself acknowledged, knowledge of off-label use on its own is insufficient to establish criminal misbranding, the act of introducing the product into commerce with such knowledge cannot be the *actus reus*. Nor can internal company documents fill that gap. *Supra* p. 6.

To satisfy fundamental Fifth Amendment principles, moreover, the proper *actus reus* would need to be established clearly by the government, and the jury would need to be instructed in such a way that it understood both what the *actus reus* was and on what evidence it could ap-

propriately rely to prove it. That standard was not satisfied here. Protected speech itself was the *actus reus*, and that is precisely what the First Amendment proscribes. *See Sorrell*, 564 U.S. at 567; *Caronia*, 703 F.3d at 168.

CONCLUSION

Defendants' motion for a judgment of acquittal or a new trial should be granted.

September 17, 2016

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on September 19, 2016, this document filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non-registered participants.

/s/ Joan McPhee

Appendix: Timeline of MIWG Engagement with FDA

- **April 3, 2007:** Meeting with FDA Commissioner von Eschenbach and others to discuss the provision of truthful, non-misleading information on new uses

- **April 18, 2008:** Comment on Draft Guidance: "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" (available here: https://www.regulations.gov/document?D=FDA-2008-D-0053-0064)

- **April 15, 2010:** Comment responding to Federal Register Notice re: FDA Transparency Task Force (available here: https://www.regulations.gov/document?D=FDA-2009-N-0247-0216)

- **October 27, 2010:** Meeting with DDMAC Director Tom Abrams and others to discuss scientific exchange and responses to unsolicited requests

- **March 17, 2011:** Meeting with FDA Chief Counsel Ralph Tyler and others to discuss medical communication issues

- **July 5, 2011:** Citizen Petition (available here: https://www.regulations.gov/document?D=FDA-2011-P-0512-0001)

- **March 27, 2012:** Comment responding to Federal Register Notice re: "Communications and Activities Related to Off Label Uses of Marketed Products and Use of Products Not Yet Legally Marketed;" Comment on Draft Guidance: "Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices" (available here: https://www.regulations.gov/document?D=FDA-2011-N-0912-0015)

- **March 1, 2013:** Comments submitted to Docket Nos. FDA-2011-P-0512 and FDA-2011-D-0868 regarding *FCC v. Fox Television Stations Inc*., and *United States v. Caronia* (available here: https://www.regulations.gov/document?D=FDA-2011-D-0868-0037)

- **July 16, 2013:** Comment responding to Federal Register Notice re: CDER Medical Policy Council (available here: https://www.regulations.gov/document?D=FDA-2013-N-0206-0007)

- **Sept. 3, 2013:** Citizen Petition (available here: https://www.regulations.gov/document?D=FDA-2013-P-1079-0001)

- **Nov. 20, 2013:** Comment on Food and Drug Administration Safety and Innovation Act Section 907 Report (available here: https://www.regulations.gov/document?D=FDA-2013-N-0745-0012)

- **April 14, 2014:** Comment on Draft Guidance: "Fulfilling Regulatory Requirements for Postmarketing Submissions of Interactive Promotional Media for Prescription Human and Animal Drugs and Biologics" (available here: https://www.regulations.gov/document?D=FDA-2013-N-1430-0018)

- **May 2, 2014:** Comments on Draft Guidance: "Distributing Scientific and Medical Publications on Unapproved New Uses – Recommended Practices" (available here: https://www.regulations.gov/document?D=FDA-2008-D-0053-0153)

- **Sept. 16, 2014:** Comment on Draft Guidance: "Internet/Social Media Platforms with Character Space Limitations – Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices" (available here: https://www.regulations.gov/document?D=FDA-2014-D-0397-0011); Comment on Draft Guidance: "Internet/Social Media Platforms: Correcting Independent Third-Party Misinformation About Prescription Drugs and Medical Devices" (available here: https://www.regulations.gov/document?D=FDA-2014-D-0447-0009)

- **October 31, 2014:** White Paper: "Systemic, Societal, and Legal Developments Require changes to FDA's Regulation of Manufacturer Speech" (available here: https://www.regulations.gov/document?D=FDA-2013-P-1079-0006); Memorandum Re: "Use of Health Care Economic Information under Section 114 of the Food and Drug Administration Modernization Act" (available here: https://www.regulations.gov/document?D=FDA-2013-P-1079-0007)

- **November 6, 2014:** Meeting with Associate Commissioner for Policy Leslie Kux to discuss MIWG proposals

- **November 24, 2015:** Comment on Proposed Rule: Clarification of When Products Made or Derived from Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses" (available here: https://www.regulations.gov/document?D=FDA-2015-N-2002-1876)

- **April 28, 2016**: Meeting with Associate Commissioner for Policy Leslie Kux to discuss MIWG proposals