

EXHIBIT A

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

PACIRA PHARMACEUTICALS, INC., DR.
LOREN J. HARRIS, and DR. JOSEPH W. BELL,

Plaintiffs,

v.

UNITED STATES FOOD & DRUG
ADMINISTRATION; UNITED STATES OF
AMERICA; DR. STEPHEN OSTROFF, in his
official capacity as Acting Commissioner of Food
and Drugs; UNITED STATES DEPARTMENT OF
HEALTH & HUMAN SERVICES; and SYLVIA
MATHEWS BURWELL, in her official capacity as
Secretary of the Department of Health & Human
Services,

Defendants.

Civil Action No. 1:15-cv-07055-ER

**BRIEF OF THE MEDICAL INFORMATION WORKING GROUP
AS *AMICUS CURIAE* IN SUPPORT OF PLAINTIFFS**

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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 for *amicus curiae*, the Medical Information Working Group (“MIWG”), a private non-governmental entity composed of major manufacturers of prescription drugs, biologics, and medical devices, certifies that the following members of the MIWG are submitting this brief: Amgen Inc., Bayer Healthcare Pharmaceuticals, Inc., Boehringer Ingelheim Pharmaceuticals, Inc., Eli Lilly and Company, Genentech, Inc., GlaxoSmithKline LLC, Johnson & Johnson, Novartis Pharmaceuticals Corporation, Novo Nordisk, Inc., Pfizer Inc., and sanofi-aventis U.S. LLC.

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

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- 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%.

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STATEMENT OF INTEREST OF *AMICUS CURIAE*

The Medical Information Working Group (“MIWG”) is an informal working group of major manufacturers of prescription drugs, biologics, and medical devices. The MIWG was formed in 2006 to improve the federal regulatory framework and enforcement climate affecting manufacturer dissemination of information about prescription drugs, biological products, and medical devices, including information about new uses of approved products. The MIWG and its members have made numerous submissions to FDA, including two citizen petitions (in 2011 and 2013) requesting clarification of, and substantive changes to, the existing regulatory framework.

In particular, the MIWG has sought to address concerns that the present regulatory framework, characterized by unclear rules and harsh penalties, fails to provide adequate notice of the line between permissible and impermissible speech and, as a result, impermissibly chills manufacturer dissemination of valuable scientific information. The risk of improperly chilling constitutionally protected speech has become even more pronounced given the Department of Justice’s recent announcement that it is focusing enhanced effort on investigating and prosecuting individuals for alleged corporate wrongdoing. *See* Memorandum of S. Yates, Deputy Attorney General, *Individual Accountability for Corporate Wrongdoing* 1-2 (Sept. 9, 2015) (noting importance of DOJ “fully leverag[ing] its resources” to target individuals), available at <http://www.justice.gov/dag/file/769036/download>. Consistent with this mission, the MIWG has a strong interest in the issues presented here.

The MIWG participated as *amicus curiae* in *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012), and *Amarin Pharma, Inc. v. FDA*, No. 15-3588 (PAE), 2015 WL 4720039 (S.D.N.Y. Aug. 7, 2015)—two leading cases addressing constitutional protection for truthful, non-misleading speech about off-label uses of FDA-approved pharmaceuticals. The MIWG also has

engaged directly with FDA on numerous occasions urging the agency to address these problems and to provide regulatory clarity. Accordingly, the MIWG brings substantial experience and perspective to bear on issues central to this case.

ARGUMENT

The MIWG writes separately as *amicus curiae* to underscore the importance of its members having the freedom to disseminate truthful, non-misleading information about their products to prescribers, payors, and patients for the benefit of patient care, without fear of civil and criminal penalty. In *United States v. Caronia*, the Second Circuit made clear that the First Amendment protects a manufacturer's right to make truthful and non-misleading promotional statements about the lawful off-label uses of its products. 703 F.3d 149, 168 (2d Cir. 2012). Thereafter, the government neither sought reconsideration nor filed a petition for *certiorari* seeking to reverse *Caronia*. That *Caronia* means what it says—notwithstanding the government's arguments to the contrary—was underscored recently in an extensive decision by Judge Engelmayer in *Amarin Pharma, Inc. v. FDA*, No. 15-3588 (S.D.N.Y. Aug. 7, 2015).

Under the principles explained in those decisions, the government's attempt to restrict protected speech must satisfy heightened scrutiny. The ambiguous tangle of regulations, non-binding guidance documents, and severe enforcement practices that form the backbone of the government's speech restrictions leave manufacturers without clear guidance and thus cannot satisfy this standard.

The question presented in this case is at least as compelling as that presented in *Caronia* and *Amarin*: Because a company's truthful, non-misleading speech about *off-label* uses of its approved product is constitutionally protected, as was the case in *Caronia* and *Amarin*, *a fortiori* a company's truthful, non-misleading speech about arguably *on-label* uses also should be protected. Pacira's position is that it seeks to share with physicians truthful, non-misleading

scientific promotional information about its pharmaceutical drug Exparel that it maintains is within those uses for which Exparel is approved, and for which its labeling provides adequate directions. Specifically, the information Pacira wishes to share would advise physicians about a matter of significant interest to physicians and their patients: the use of Exparel to alleviate patients' post-operative pain in various surgical sites. Nonetheless, three years after marketing began, FDA sent Pacira a Warning Letter, threatening that such communications should "immediately cease" because they render Exparel misbranded in violation of federal law. Warning Letter, Helisek Decl., Ex. 2 at 1, 4-5.

In speech regulation, the Constitution requires a precision that is belied by the uncertainty inherent in the current regulatory and enforcement regime. In this environment, would-be speakers refrain from disseminating highly valuable information about lawful on- and off-label uses of medical products that could benefit physician decision-making and patient care. This chilling effect is constitutionally intolerable. It is not for the government to restrict the flow of truthful and non-misleading information.

I. A MANUFACTURER'S TRUTHFUL AND NON-MISLEADING SPEECH ABOUT LAWFUL USES OF FDA-APPROVED PRODUCTS IS HIGHLY VALUABLE AND PROTECTED BY THE CONSTITUTION.

The vital issue at the case's core is that FDA seeks to limit, by threat of criminal prosecution, the truthful and non-misleading information Pacira relays to the physicians who prescribe its products. When speakers disseminate truthful and accurate information in a non-misleading fashion, they do so under the protection of the First Amendment's Free Speech Clause. As a result, FDA's attempts to prevent Pacira from communicating with physicians in this manner face heightened judicial scrutiny, a hurdle it cannot clear. Moreover, FDA's practice of chilling this speech impedes the flow of valuable, pain-alleviating, and potentially life-saving information to physicians about lawful activity.

A. It Is Now Well Established In This Circuit That The Constitution Protects A Manufacturer’s Truthful And Non-Misleading Speech About Lawful Uses Of FDA-Approved Products.

Familiar constitutional boundaries limit FDA’s ability to regulate what manufacturers can and cannot say about their approved products. As the United States Supreme Court has explained, because “[s]peech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment,” content- and speaker-based restrictions on such speech face “heightened judicial scrutiny.” *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653, 2659 (2011). To be sure, where a manufacturer’s speech is “likely to deceive the public,” or uttered to foment “illegal activity,” the “government may ban [such] forms of communication.” *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm’n of New York*, 447 U.S. 557, 563-64 (1980). But where a manufacturer speaks truthfully, and in a non-misleading fashion, about how its approved products may be lawfully used, “the government’s power is more circumscribed.” *Id.* at 564. In such an instance, a restriction—whether “burdening” or “banning” the manufacturer’s speech—must “advance a substantial government interest” and be carefully “drawn to achieve that interest.” *Sorrell*, 131 S. Ct. at 2664, 2667-68 (internal quotation omitted). Where “a more limited restriction” would suffice, “excessive restrictions cannot survive.” *Cent. Hudson*, 447 U.S. at 564.

The Second Circuit has addressed the application of these principles in the context of off-label speech about lawful uses of FDA-approved products. In *Caronia*, the Second Circuit rejected the government’s attempt to treat truthful and non-misleading promotional claims by a manufacturer’s sales representative about approved products as criminal misbranding under the FDCA. 703 F.3d at 168. The defendant, an individual company sales representative, was convicted of criminal misbranding for promoting “unapproved uses” of the pharmaceutical drug Xyrem to physicians in a manner the government conceded was neither false nor misleading. *Id.*

at 156, 165 & n.10. The Second Circuit vacated the criminal conviction. In so doing, the court explained that the government’s “content- and speaker-based” suppression of protected communications raised serious “First Amendment concerns” and rejected the government’s notion that its interpretation was necessary to its regulation of pharmaceuticals under the FDCA. *Id.* at 160, 165. Thus, “criminalizing the truthful off-label promotion of FDA-approved prescription drugs” violates the Constitution. *Id.* at 168.

As *Caronia* chronicled, for years “[t]he government has repeatedly prosecuted—and obtained convictions against—pharmaceutical companies and their representatives for misbranding,” often based on constitutionally protected communications. *Id.* at 154. Likewise, the government has relied on warning letters to secure “voluntary” compliance with its interpretation of the law by threatening criminal prosecution and civil consequences. *Caronia* made clear the constitutional impropriety of such an expansive enforcement approach.

The government did not seek further review of *Caronia*, instead taking the tack that the case was limited to its facts, and continuing its prior enforcement approach. In *Amarin*, Judge Engelmayer *rejected* FDA’s attempt to construe *Caronia* as merely “a fact-bound decision that turned on the particular jury instructions and government jury addresses given in Caronia’s trial.” 2015 WL 4720039, at *22. In that case, FDA had issued a letter to Amarin, “reserving the right to bring a misbranding action . . . where the only conduct on which that action would be based are truthful and non-misleading statements promoting . . . off-label use.” *Id.* Amarin sought a preliminary injunction. Judge Engelmayer’s “considered and firm view [was] that, under *Caronia*, the FDA may *not* bring such an action based on truthful promotional speech alone, consistent with the First Amendment.” *Id.* at *23 (emphasis original).

Given “[t]he Second Circuit’s thoroughgoing First Amendment analysis” and “the categorical, rather than case-specific” holding it announced, Judge Engelmayer rejected “FDA’s attempt to marginalize [*Caronia*’s] holding . . . as fact-bound.” *Id.* at *24; *see also id.* at *25 (“This Court therefore rejects the FDA’s reading of *Caronia* as a mere artifact of that case’s particular facts and circumstances.”); *id.* at *26 n.57 (“This Court cannot override the Second Circuit’s definitive construction of the misbranding statute.”). Finding that Amarin “established a substantial likelihood of success on the merits” of its First Amendment claim, *id.* at *25, the court barred FDA from pursuing the course it had threatened: “Where the speech at issue consists of truthful and non-misleading speech promoting the off-label use of an FDA-approved drug, such speech, under *Caronia*, cannot be the act upon which an action for misbranding is based.” *Id.* (emphasis original).

Unfortunately, as this case illustrates, FDA continues to take a different view of the established law of this Circuit. The result is a troubling lack of clarity about what manufacturers may say about on- and off-label uses of their FDA-approved products.

B. A Manufacturer’s Truthful And Non-Misleading Speech About Lawful Uses Of Its Products, Whether On- Or Off-Label, Supplies Valuable Medical Information.

The Constitution’s protection of truthful and non-misleading speech about FDA-approved products is no mere formality. As the Supreme Court has noted, “the 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*, 131 S. Ct. at 2664. Moreover, because “manufacturers have superior access to information about their drugs,” *Wyeth v. Levine*, 555 U.S. 555, 578-79 (2009), they are frequently best-positioned to disseminate

it. Restricting the role of manufacturers in the informational marketplace not only is impermissibly discriminatory, but it also degrades the quality of information accessible to doctors, patients, and payors.

The facts of this case offer an illustration. As Pacira explains, Exparel provides physicians with a powerful tool to manage pain following surgery. Significantly, it offers physicians and their patients an alternative to opioid pain relievers. As the Department of Health and Human Services recently recognized, “overdoses from prescription opioid pain relievers claimed more than 16,200 lives” in 2013 alone, “with more than 145,000 people dying from these overdoses in the last decade.” Dep’t of Health & Human Services, *HHS hosts 50-state convening focused on preventing opioid overdose and opioid use disorder, takes important step to increase access to treatment* (Sept. 17, 2015), available at <http://www.hhs.gov/news/press/2015pres/09/20150917a.html> (last visited Oct. 15, 2015). While opioids (such as morphine) remain among the most effective and widely prescribed pain relievers, physicians and researchers have recognized that “chronic use can lead to addiction and negative side effects.” Mount Sinai Hosp., *Chemical Compound Shows Promise as Alternative to Opioid Pain Relievers* (July 1, 2013), available at <http://www.mountsinai.org/about-us/newsroom/press-releases/chemical-compound-shows-promise-as-alternative-to-opioid-pain-relievers> (last visited Oct. 15, 2015). Indeed, FDA has pledged to “continue to work hard to address the serious problem of opioid abuse while providing needed pain medicines for patients.” Janet M. Woodcock, M.D., *Additional progress on reducing the abuse of opioid pain relievers*, FDA Voice (Nov. 20, 2014), available at <http://blogs.fda.gov/fdavoices/index.php/2014/11/additional-progress-on-reducing-the-abuse-of-opioid-pain-relievers/> (last visited Oct. 15, 2015).

At issue here is Pacira's effort to disseminate what it contends is truthful and non-misleading *on-label* information about one non-opiate option for relieving pain following surgery.

FDA maintains, however, that such an exchange of information constitutes criminal misbranding. To the extent there is ambiguity about whether FDA previously has approved a safety or efficacy claim, FDA apparently views that information as constituting potentially actionable misbranding. *See generally Washington Legal Found. ["WLF"] v. Friedman*, 13 F. Supp. 2d 51, 67 (D.D.C. 1998), *appeal dismissed, judgment vacated on other grounds*, 202 F.3d 331 (D.C. Cir. 2000) ("In asserting that any and all scientific claims about the safety, effectiveness, contraindications, side effects, and the like regarding prescription drugs are presumptively untruthful or misleading until the FDA has had the opportunity to evaluate them, FDA exaggerates its overall place in the universe."). The Constitution does not, however, require that the government pre-approve all truthful and non-misleading information before it may be communicated. To the contrary, "[t]he First Amendment directs us to be especially skeptical of regulations that seek to keep people in the dark for what the government perceives to be their own good." *Sorrell*, 131 S. Ct. at 2671 (quoting *44 Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 503 (1996) (opinion of Stevens, J.)).

The government's restrictive efforts are especially troubling where the speech at issue is on-label, and therefore already FDA-approved. Even under the government's narrow view of First Amendment protection, at a minimum, a manufacturer should be able to count on a safe harbor for speech about on-label uses. Here, for example, it is Pacira's contention that it received a general indication in its labeling for the relief of post-surgical pain relief that was not limited to a particular surgical site. Yet, three years after the drug's approval, FDA sent the company a Warning Letter taking the position that only two specific surgical sites are on-label,

and speech about other surgical sites is off-label and unlawful. This lack of clarity and consistency inevitably chills valuable speech.

Moreover, even if the information at the heart of this case *did* concern truthful and non-misleading speech about off-label uses of Exparel, such speech still would be protected. A manufacturer's dissemination of information is no less valuable—nor any less protected—when it concerns off-label uses of approved products. It has become axiomatic that “off-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 is not a regulatory gap. 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).

Off-label prescription by a qualified health care professional can significantly enhance patient care. 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 American Academy of Pediatrics, Committee on Drugs, Uses of Drugs Not Described in the Package Insert (Off-Label Uses)*, 110 *Pediatrics* 181, 182 (2002) (“AAP”). In fact, as FDA itself recognizes, off-label use is so ubiquitous that it “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) (“Draft Guidance on Unsolicited Requests”), available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm285145.pdf> (last visited Oct. 15, 2015); 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>. Recognizing the importance of off-label use to patient care, federal law even 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). This is especially true in the case of serious illnesses, such as cancer. *Id.* Moreover, the safety and efficacy of an off-label use is no guarantee of its eventual approval. Many factors will affect whether the FDA-approval process may be undertaken for all possible uses of a product.

Given these critical public health considerations, *more* truthful and non-misleading information about off-label uses is better than *less*. See *Caronia*, 703 F.3d at 167 (“[I]t only furthers the public interest to ensure that decisions about the use of prescription drugs, including off-label usage, are intelligent and well-informed.”); 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? The billions of dollars in corporate fines

flowing into government coffers or absorbed by legal fees, which might otherwise be put to good use in discovering new medicines, compel us to question the wisdom of government policy in this area.”). To restrict a manufacturer’s ability truthfully to provide valuable information to those who need it the most runs counter not only to common sense, but also to the principles undergirding the First Amendment.¹ As the Seventh Circuit aptly described:

[I]f a given use is lawful, and thus can be written about freely in newspapers or blogs, and discussed among hospitals that already have purchased [the product], doesn’t it make a good deal of sense to allow speech by the [product]’s manufacturer, which after all will have the best information? Why privilege speech by the uninformed?

United States v. Caputo, 517 F.3d 935, 939 (7th Cir. 2008). Simply put: “Compelling private persons to toe the government’s line, or shut up, is unconstitutional.” *Id.* Moreover, if the government has a different view on the topic at hand, it may always disseminate that information “via its own speech.” *Id.*

These principles are all the more powerful here given Pacira’s argument that the information it wishes to provide is within the four corners of the FDA-approved labeling—so it is simply supplying on-label information. Even under the government’s view, on-label speech is undoubtedly “speech about the government-approved use of drugs” and therefore “permitted.” *Caronia*, 703 F.3d at 165. But even if the information at issue were off-label, provided it is truthful and non-misleading, it also is protected by the Constitution, just as the off-label speech was in *Caronia* and *Amarin*.

¹ Indeed, it is beyond peradventure that the Constitution generally favors more speech, rather than government-enforced silence. See generally *Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc.*, 425 U.S. 748, 770 (1976) (preferred constitutional approach is “to open the channels of communication rather than to close them”); *Linmark Associates, Inc. v. Twp. of Willingboro*, 431 U.S. 85, 97 (1977) (“[T]he remedy to be applied is more speech, not enforced silence. Only an emergency can justify repression.”) (quoting *Whitney v. California*, 274 U.S. 357, 377 (1927) (Brandeis, J., concurring)).

II. THE CURRENT REGULATORY AND ENFORCEMENT ENVIRONMENT IMPROPERLY CHILLS CONSTITUTIONALLY PROTECTED AND MEDICALLY VALUABLE SPEECH, DEPRIVING SOPHISTICATED PHYSICIANS OF INFORMATION THAT IS CRITICAL TO PATIENT CARE.

To prevent the chilling of constitutionally protected speech, the government must provide clear guidance on the line separating permissible and impermissible speech. The current lack of clarity, and consistency, falls well short of this standard. Unfortunately, the current environment is marked by unclear, and shifting, standards. Yet the penalties for violation are so severe that manufacturers historically have had little practical choice but to yield to the government's expansive interpretation of the scope of its own regulatory power.

A. Content- And Speaker-Based Restrictions That Threaten To Impose Criminal Penalties Must Be Clear And Precise To Be Constitutional.

When the government restricts protected speech based on either the content of the speech or the identity of the speaker, it faces “heightened judicial scrutiny.” *Sorrell*, 131 S. Ct. at 2659; accord *Caronia*, 703 F.3d at 164-65 (noting that “[t]he government’s construction of the FDCA’s misbranding provisions . . . is content- and speaker-based, and, therefore, subject to heightened [judicial] scrutiny”). *Caronia* makes clear that this standard applies to restrictions FDA seeks to impose here.

In *Caronia*, the Second Circuit characterized the government’s prosecution as content-based, “because it distinguishes between favored speech and disfavored speech on the basis of the ideas or views expressed.” *Id.* at 165 (internal quotation omitted). Because the government would permit “speech about the government-approved use of drugs,” while disallowing speech about lawful off-label uses, “the content of the regulated speech” improperly drove the prohibition. *Id.*; see also *Sorrell*, 131 S. Ct. at 2663 (classifying restrictions as content-based when they “disfavor[] marketing”). Likewise, the government’s prosecution of *Caronia* was

“speaker-based because it target[ed] one kind of speaker—pharmaceutical manufacturers—while allowing others to speak without restriction” about the same matters. *Caronia*, 703 F.3d at 165.

The same dynamic characterizes FDA’s threatened prosecution of Pacira. The Warning Letter specifically references “educational technique flashcards” and “a journal ad” released by Pacira that “provide evidence that Exparel is intended for new uses for which it lacks approval.” *See* Warning Letter, Helisek Decl., Ex. 2 at 1. Concluding that these communications rendered Exparel “misbranded,” FDA demanded that Pacira “immediately cease violating the FD&C Act.” *Id.* at 4. As in *Caronia*, this interpretation of the misbranding provisions leaves “physicians and academics,” among others, free to discuss Exparel’s efficacy in precisely ways that may render Pacira criminally liable. 703 F.3d at 165. Such a restriction impermissibly targets Pacira’s speech based on both its content and its speaker. Heightened judicial scrutiny of those restrictions is the consequence.

A critical component of heightened scrutiny in the First Amendment context is the requirement that “a statute regulat[ing] the content of speech” be precise. *Reno v. ACLU*, 521 U.S. 844, 874 (1997). The “‘government may regulate in the area’ of First Amendment freedoms” only if it provides “the ‘narrow specificity’ that the Constitution demands.” *Brown v. Entert. Merch. Ass’n*, 131 S. Ct. 2729, 2743 (2011) (quoting *NAACP v. Button*, 371 U.S. 415, 433 (1963)). Motivating this judicial insistence are “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.*

B. The Speech Restrictions Here Are Neither Clear Nor Precise.

FDA's regulation of manufacturer speech lacks the requisite precision and fails to provide clear guidance to would-be speakers. On the heels of *Caronia* and *Amarin*, FDA has yet to proffer a constitutionally permissible interpretation of its authority to regulate off-label speech—much less, on-label speech. Moreover, Pacira's experience highlights the uncertainty facing manufacturers who seek to disseminate information about *on-label* uses the agency previously has recognized are protected.

As a result, the dissemination of valuable medical information about both on- and off-label uses of approved products is a risky endeavor. Even where manufacturers may disseminate information that judicial precedent assures is protected, they still face of threats of criminal and civil penalties from the government. In this environment, many manufacturers instead opt to self-censor, thereby depriving physicians and patients of important and valuable medical information.

1. FDA's Regulation Of The Dissemination Of Information Is Ambiguous.

FDA derives its purported authority to regulate truthful, non-misleading manufacturer speech not from a clear and precise statement of law, but from a labyrinth of statutes and regulations, as well as non-binding guidance documents and aggressive enforcement practices. Far from affording speakers the clear guidance the Constitution guarantees, this regime depends on conjecture and inference.

Consider, for instance, the Warning Letter received by Pacira in this case. In its conclusion section, FDA summed up its case against Pacira with a network of citations:

For the reasons discussed above, the administration guides provide evidence that Exparel is intended for new uses for which it lacks approval, and for which its labeling does not provide adequate directions for us, which renders Exparel misbranded or otherwise makes its distribution violative. *See* 21 USC 355(a),

352(f); 331(a), (d); 21 CFR 201.5; 201.100; 201.115; 201.128. The journal ad also misbrands Exparel within the meaning of the FD&C Act, and makes its distribution violative. 21 CFR 202.1(e)(6)(i).

Warning Letter, Helisek Decl., Ex. 2 at 4. Untangling these citations underscores how ambiguous the current regulatory lines are. Section 355(a) mandates FDA approval of any new drug introduced into interstate commerce. 21 U.S.C. § 355(a). Section 331(a) forbids the delivery or introduction of any drug that is “misbranded,” and Section 352(f)(1) deems “misbranded” any drug the “labeling” of which fails to provide “adequate directions for use.” *Id.* §§ 331(a), 352(f)(1). FDA’s own regulations offer little to elucidate the “adequate directions for use” standard. For instance, 21 C.F.R. § 201.5 suggests that prescription drugs can never satisfy the “adequate directions for use” standard, but 21 C.F.R. § 201.100(c)(1) exempts prescription drugs with “labeling” that bears “adequate information for its use . . . under which practitioners . . . can use the drug safely and for the purposes for which it is intended, including all purposes for which it is advertised or represented.” 21 C.F.R. §§ 201.100(c)(1), 201.5. A subsequent regulation, 21 C.F.R. § 201.128, then endeavors to define not only “[t]he words ‘intended uses’” but also any “words of similar import in” FDA’s various regulations. 21 C.F.R. § 201.128. That definition includes “the objective intent of the persons legally responsible for the labeling of drugs,” and “may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives.” *Id.*² From this, FDA asserts

² FDA previously has taken the position that intent “may be shown by the circumstances 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. § 201.128. The government previously has argued—for example, in the *Caronia* criminal misbranding trial, and just two months ago in another criminal misbranding prosecution—that mere knowledge of off-label use could be enough to justify a conviction. *See* Gov’t Requests to Charge at 18, *United States v. Caronia*, No. 06-0229 (E.D.N.Y. Sept. 2, 2008), ECF No. 77 (requesting a jury instruction, ultimately adopted by the district court, that “knowledge” that a drug will be prescribed off-label could support a violation of the misbranding provisions); Gov’t Opp. to Defs’ Mot. for

authority to treat truthful speech about the lawful use of products as evidence of an “intended use” beyond the scope of FDA’s approval, and thus evidence of criminal misbranding. *See Caronia*, 703 F.3d at 161.

This prohibition may be difficult to grasp in theory, but more importantly, it is even harder to abide in practice. If the representatives of “those legally responsible for the labeling of drugs” can evince an “objective intent” criminally to misbrand drugs by their mere “expressions” or by “the circumstances surrounding the distribution,” it is difficult to imagine what communication FDA could *not* target. 21 C.F.R. § 201.128; *see also Caronia*, 703 F.3d at 162 n.9 (noting that it “still remains unclear how the government would identify criminal misbranding from communications between drug manufacturers and physicians authorized to prescribe drugs for off-label use”). The precise contours of those “expressions” and “circumstances” that may be taken as evidence of an objective intent to violate federal law remains unclear. This state of affairs “fails to clearly mark the boundary between permissible and impermissible speech.” *Buckley v. Valeo*, 424 U.S. 1, 41 (1976); *accord FCC*, 132 S. Ct. at 2317 (“When speech is involved, rigorous adherence to [fair notice] requirements is necessary to ensure that ambiguity does not chill protected speech.”).

Consequently, an extraordinarily wide range of communications remain susceptible to misbranding charges. For example, under a plain reading of § 201.128, an “objective intent” to

Production of Legal Instructions to Grand Jury at 13-14, *United States v. Facticeau, Fabian*, No. 15-CR-10076 (D. Mass. Aug. 6, 2015), ECF No. 101.

On September 25, 2015, FDA published in the Federal Register a proposal to amend its existing “intended use” regulations for drugs and medical devices. The proposal would remove language defining “intended use” to include a manufacturer’s mere knowledge that its product is to be used off-label—a revision MIWG has urged for years in its citizen petitions to the agency. Even this revision, however, would not ameliorate the larger constitutional problems identified here.

misbrand may “be shown by . . . oral or written statements by [a manufacturer’s] representatives,” without any limitation. This would seem to preclude a representative from saying *anything* in an official capacity regarding uses not squarely within FDA’s conception of the product’s FDA-approved labeling—even when off-label use is the accepted standard of care. “No speaker, in such circumstances, safely could assume that anything he might say upon the general subject would not be understood” to be misbranding. *Buckley*, 424 U.S. at 43. The circumstances of this case present such an example. Under Pacira’s view, FDA approved its product for use across post-surgical sites, yet when the company provided truthful and non-misleading information about those on-label uses, FDA’s response was to issue a Warning Letter seeking to stop all such communications.

In such a climate, regulatory compliance is often reduced to guesswork. And where a “person seeking to communicate his or her point of view . . . cannot know in advance whether the [government] will read the communication” as violative, the prohibition on speech is “impermissibly vague.” *Vt. Right to Life Comm., Inc. v. Sorrell*, 221 F.3d 376, 387 (2d Cir. 2000). As the Supreme Court has noted, “[t]he prohibition against vague regulations of speech is based in part on the need to eliminate the impermissible risk of discriminatory enforcement.” *Gentile v. State Bar of Nev.*, 501 U.S. 1030, 1051 (1991). A case like Pacira’s only compounds the danger of this imprecision. When a manufacturer is unable to determine not only the boundary of permissible communication, but the boundary of on-label use as well, all but the most rote discussion of the product is stifled.

2. The Purported “Safe Harbors” Are Arbitrary And Do Not Clarify The Regulatory Scheme.

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. But, beyond this, manufacturers are left to divine what information may lawfully be shared from guidance documents that “do[] not purport to be binding on the enforcement authorities.” *Hynes v. Borough of Oradell*, 425 U.S. 610, 622 n.6 (1976). Reliance on such sources would be perilous enough, but the problem is exacerbated by the agency frequently changing course without warning. For example, FDA once opined in a guidance document that manufacturers were free to distribute reprints detailing pivotal studies. *See Advertising and Promotion; Guidances*, 61 Fed. Reg. 52,800 (Oct. 8, 1996). That document has since vanished from FDA’s website and no longer appears on the agency’s list of effective guidance documents. The legal status of its contents is ambiguous. Moreover, the agency has taken inconsistent positions on whether “scientific exchange” is one safe harbor for manufacturer speech regarding off-label uses, or a generic term used to describe several. *Compare, e.g.*, Final Guidance of Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64,074, 64,095-96 (Dec. 3, 1997), *and* 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) (“Good Reprint Practices”), *available at* <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm> (last visited Oct. 15, 2015) (suggesting that “scientific exchange” is the only safe harbor), *with* Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Treatment Use and Sale, 52 Fed. Reg. 19,466, 19,475 (May 22, 1987) (suggesting “scientific exchange” represents one of several safe harbors).

Unfortunately, guidance documents offer only limited insight and often fail to clarify or discuss those issues that are most important to manufacturers. For instance, with respect to a

manufacturer's distribution of scientific journal article "reprints" covering off-label uses, FDA cautions against including "information that is promotional in nature," without defining the sort of information it considers promotional. Good Reprint Practices. When providing guidance on how to respond to unsolicited requests for information on unapproved uses, FDA states that such a response may include "non-promotional scientific or medical information," while again failing to further define "promotional." Draft Guidance on Unsolicited Requests at 6. This omission is critical. The line between what is and what is not "promotional" is of the utmost importance to manufacturers. Yet, in the current environment, that line is unclear and relegated to the post-hoc *ipse dixit* of the reviewing agency official.

Nor have manufacturers been able to secure the necessary clarification through either formal or informal exchange with FDA. Indeed, in informal communication with requesters, FDA 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). The MIWG has asked the agency to implement a binding advisory process under 21 C.F.R. § 10.85(a), in place of the current non-binding advisory comment process under 21 C.F.R. § 201.1(j)(4), to provide timely advice in response to specific requests regarding proposed promotions, but to no avail. Manufacturers often fare no better seeking informal guidance, as the facts of this case demonstrate. Indeed, despite its numerous submissions and requests to discuss with FDA the scientific evidence supporting its claims about Exparel, Pacira was largely ignored.

C. Without Clear Guidelines, Manufacturers Have No Choice But To Cease Protected Communication.

The ambiguity of the current regulatory and enforcement environment results in a constitutionally intolerable chill on important speech. Unfortunately, the agency's view of

speech restrictions often is first presented to a manufacturer in the context of a warning or untitled letter. Such letters typically direct the manufacturer to cease all communication FDA deems violative, (in the case of Warning Letters) under threat of enforcement action. *See, e.g.*, Warning Letter, Helisek Decl., Ex. 2 at 5 (“Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.”). The government has overwhelming leverage in these interactions, a dynamic that almost invariably prompts manufacturers to comply with FDA’s demands, even at the expense of protected communication.

In fact, “in some cases the agency has advised government purchasing entities not to deal with the recipient until the matter [in the warning letter] is addressed.” Jerry Brito, *Executive Discretion And The Rule Of Law: “Agency Threats” and the Rule of Law: An Offer You Can’t Refuse*, 37 Harv. J.L. & Pub. Pol’y 553, 562 n.47 (2014). And, “[b]ecause the federal government is the largest purchaser of prescription drugs in the country, recipients often can do little but comply.” *Id.* Defending against an enforcement action would impose costs that, even if the manufacturer were ultimately to prevail, would yield irreparable harm. Indeed, simply receiving a warning letter can be costly. *See* Katelyn Deruyter, *Does Sackett Foreshadow the End of Non-Reviewability for FDA Warning Letters?*, 68 Food Drug L.J. 241, 243-44 (2013) (noting that warning letters “have the practical effect of imposing penalties on recipients,” and have “been linked to reduction in stock value”).

Manufacturers seeking to disseminate truthful, non-misleading information about lawful uses of their products to sophisticated parties are protected by the First Amendment. Yet the government’s regulations, and its practices and enforcement methods, render the boundary of that protection too obscure to identify and too untenable to test.

III. THERE IS A COMPELLING NEED FOR JUDICIAL REVIEW OF THE IMPORTANT CONSTITUTIONAL AND STATUTORY ISSUES AT STAKE.

When an aggressive enforcement regime meets an ambiguous regulatory climate, the byproduct is chilled speech. Not only does the threat of penalty stifle communication, it also enables the government to evade judicial review of its restrictions as warning letters have not been considered final agency action. This Court’s review in this case is vital to ensure that protected communication by Pacira is not chilled.

A. Judicial Review Is Proper Because FDA Is Chilling Protected First Amendment Communications By Threatening Criminal Penalty.

This Court’s review is necessary because communication protected by the First Amendment is at stake. In the Second Circuit, courts “assess pre-enforcement First Amendment claims . . . under somewhat relaxed standing and ripeness rules.” *Nat’l Org. for Marriage v. Walsh*, 714 F.3d 682, 689 (2d Cir. 2013). While “[a] plaintiff must allege something more than an abstract, subjective fear that his rights are chilled in order to establish a case of controversy[,] . . . a real and imminent fear of such chilling is enough.” *Id.* (citation omitted). Indeed, “without the possibility of pre-enforcement challenges, plaintiffs contesting statutes or regulations on First Amendment grounds ‘face an unattractive set of options if they are barred from bringing a facial challenge’: refraining from activity they believe the First Amendment protects, or risk civil or criminal penalties for violating the challenged law.” *Id.* (quoting *Fla. League of Prof’l Lobbyists, Inc. v. Meggs*, 87 F.3d 457, 459 (11th Cir. 1996)). As one court put it: “[i]n an effort to avoid the chilling effect of sweeping restrictions, the Supreme Court has endorsed what might be called a ‘hold your tongue and challenge now’ approach rather than requiring litigants to speak first and take their chances with the consequences.” *Ariz. Right to Life Political Action Comm. v. Bayless*, 320 F.3d 1002, 1006 (9th Cir. 2003). These principles apply not only to criminal prosecutions, where an individual’s very liberty is placed in jeopardy, but also “in the

civil context as well.” *Hedges v. Obama*, 724 F.3d 170, 196-97 (2d Cir. 2013). Especially in the pharmaceutical industry, “[t]he fear of civil penalties can be as inhibiting of speech as can trepidation in the face of threatened criminal prosecution.” *Vt. Right to Life Comm.*, 221 F.3d at 382 (citation omitted).

Against this backdrop, and in similar circumstances, Judge Engelmayer found judicial review appropriate in *Amarin*. There, “the Complaint alleged that Amarin wishes to make truthful statements to healthcare professionals . . . regarding Vascepa,” including statements related to the results of a scientific study. *Amarin*, 2015 WL 4720039, at *12. However, Amarin alleged, “it is inhibited from doing so by the FDA’s threat . . . to bring a misbranding action based on such . . . promotion.” *Id.* Judge Engelmayer found Amarin “clearly has standing to challenge the FDA’s threat,” because “Amarin faces a non-extinguished threat of . . . prosecution for speech it proposes to undertake.” *Id.* at *20, 21.

Pacira faces that same threat. The risk involved in defending an enforcement action has forced Pacira to refrain from the communication at issue. But it has made clear to FDA its belief that the communication is protected and permissible, not only because it promotes *on*-label use, but because even if it did not, it still would be protected by the First Amendment. Much like Amarin, Pacira faces an untenable choice of constitutional dimensions. This Court’s review is thus critical.

B. This Court’s Review Will Ensure That A Regulatory Regime With A Significant Potential To Chill Protected Speech Cannot Evade Judicial Review.

In addition to ensuring that Pacira’s protected speech is not chilled, this Court’s review will ensure that FDA cannot evade scrutiny of its regulatory and enforcement regime. For years, the government’s enforcement practices had effectively insulated the regulatory and enforcement scheme from judicial review. Given the extraordinary stakes for companies and their

personnel—including the prospect of jail and the threat of exclusion from participating in the government’s healthcare programs—off-label marketing investigations commenced by the Department of Justice often are settled out of court, often for astronomical sums.³

In pre-enforcement free speech cases such as this one, the government has fought against judicial review on standing and ripeness grounds. *See, e.g.*, Defendants’ Br. at 12-19, *Par Pharm., Inc. v. United States*, No. 1:11-cv-1820 (D.D.C. Jan. 11, 2012), ECF No. 14-1; Defendants’ Br. at 13-16, *Allergan, Inc. v. United States*, No. 09-1879 (D.D.C. Dec. 11, 2009), ECF No. 18. In other cases, the government has urged a lack of justiciability, and then, in response to adverse rulings upholding constitutional protections, agreed at the eleventh hour to a “safe harbor” to evade appellate review. *Compare WLF v. Friedman*, 13 F. Supp. 2d at 67 (D.D.C. 1998), *and WLF v. Henney*, 56 F. Supp. 2d 81, 88-89 (D.D.C. 1999) (enjoining various FDA restrictions on off-label speech as unconstitutional), *with WLF v. Henney*, 202 F.3d 331, 335-36 (D.C. Cir. 2000) (dismissing appeal after FDA “insists that nothing in either of the provisions challenged in this case provides the FDA with independent authority to regulate manufacturer speech” and “vacat[ing] the district court’s decisions and injunctions insofar as they declare the [speech restrictions] unconstitutional”). And, in *Amarin*, the government raised

³ *See, e.g.*, Press Release, Dep’t of Justice, Shire Pharmaceuticals LLC to Pay \$56.5 Million to Resolve False Claims Act Allegations Relating to Drug Marketing and Promotion Practices (Sept. 24, 2014), *available at* <http://www.justice.gov/opa/pr/shire-pharmaceuticals-llc-pay-565-million-resolve-false-claims-act-allegations-relating-drug> (last visited Oct. 15, 2015); Press Release, Dep’t of Justice, Endo Pharmaceuticals and Endo Health Solutions to Pay \$192.7 Million to Resolve Criminal and Civil Liability Relating to Marketing of Prescription Drug Lipoderm for Unapproved Uses (Feb. 21, 2014), *available at* <http://www.justice.gov/opa/pr/endo-pharmaceuticals-and-endo-health-solutions-pay-1927-million-resolve-criminal-and-civil> (last visited Oct. 15, 2015); Press Release, Dep’t of Justice, Par Pharmaceuticals Pleads Guilty and Agrees to Pay \$45 Million to Resolve Civil and Criminal Allegations Related to Off-Label Marketing (Mar. 5, 2013), *available at* <http://www.justice.gov/opa/pr/par-pharmaceuticals-pleads-guilty-and-agrees-pay-45-million-resolve-civil-and-criminal> (last visited Oct. 15, 2015).

mootness arguments in a further attempt to avoid judicial review. *See* Defendant’s Br. at 15-17, *Amarin Pharma, Inc. v. FDA*, No. 15-3588 (S.D.N.Y. June 23, 2015), ECF No. 51 (arguing “case or controversy requirement is not met” in part because “if Amarin takes the reasonable steps outlined in [FDA’s] letter,” the threat of prosecution would be abated); *but see Amarin*, 2015 WL 4720039, at *21 (noting that “although [FDA’s] Letter removed some of Amarin’s proposed communications to doctors as potential subjects of enforcement action, it left others in play”).

This state of affairs is not sustainable. When established and recognized First Amendment freedoms are at stake, judicial relief must not be reserved “only [for] those hardy enough to risk criminal prosecution” or civil sanction. *Dombrowski v. Pfister*, 380 U.S. 479, 486-87 (1965).

C. Judicial Review Is All The More Urgent Now As Recent Decisions Have Clarified The Constitutional Framework.

By clarifying that the First Amendment protects truthful and non-misleading promotional speech by manufacturers, *Sorrell* and *Caronia* cast significant doubt on the propriety of many of the government’s prior enforcement practices. The impact of these cases was confirmed by Judge Engelmayer’s thorough opinion applying *Caronia* in *Amarin*. Accordingly, the need for judicial review is even more pronounced. The government should not be permitted to continue enforcement practices shown to raise constitutional concerns and then evade judicial review in the manner it has for years.

* * *

As applied to Pacira in this case, FDA’s regulations are unconstitutional. The heightened scrutiny that attends the government’s efforts to regulate protected speech exposes an uncertain environment with an intolerable chilling effect. Despite the fact that Pacira aims only to share

truthful and non-misleading information with sophisticated physicians, the government has forced Pacira to hold its tongue. The danger of this regime “is, in large measure, one of self-censorship.” *Virginia v. Am. Booksellers Ass’n, Inc.*, 484 U.S. 383, 393 (1988). It inflicts “a harm that can be realized even without a prosecution.” *Id.* This case is about abating that harm.

CONCLUSION

For these reasons, the relief requested by the plaintiffs should be granted.

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