



Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products; Availability of Memorandum; Reopening of Comment Period (Docket No. FDA-2016-N-1149)

Comments Of The Medical Information Working Group

April 19, 2017

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April 19, 2017

Via Electronic Submission

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Re: Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products; Availability of Memorandum; Reopening of Comment Period (Docket No. FDA-2016-N-1149)

These comments are submitted on behalf of the Medical Information Working Group (MIWG), in response to the Federal Register notice published by the Food and Drug Administration (FDA) on September 1, 2016.¹ The MIWG is a coalition of medical product manufacturers focused on improving the regulatory and enforcement environment affecting manufacturer communications about drugs and medical devices, including development-stage drugs and medical devices and new uses of lawfully marketed products.² MIWG representatives testified at the November 9-10, 2016 FDA public hearing that is the subject of the September 1 notice, and our testimony is appended to this submission for convenient reference.

FDA has explained that public hearing testimony and related written submissions would “inform FDA’s policy development” as part of the agency’s comprehensive review of regulations and policies governing manufacturer communications.³ FDA first announced the comprehensive review in June 2014, in a letter granting MIWG’s citizen petitions. According to the June 2014 letter, FDA was “broadly” reviewing and analyzing its policies, guidance, and regulations in recognition of “the evolving legal landscape in the area of the First Amendment.”⁴ Yet the September 1, 2016 notice announcing the public hearing suggested FDA believed it could develop policy with respect to manufacturer communications without meaningfully considering First and Fifth Amendment limitations. The notice thus raised significant questions about FDA’s approach to the comprehensive review.

¹ Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products; Public Hearing; Request for Comments, 81 Fed. Reg. 60299 (Sept. 1, 2016) [hereinafter “Public Hearing Notice”].

² The members of the MIWG are: Allergan plc; Amgen, Inc.; Bayer Healthcare Pharmaceuticals Inc.; Boehringer Ingelheim Pharms. Inc.; Bristol-Myers Squibb Company; Eli Lilly and Company; Genentech, Inc.; GlaxoSmithKline LLC; Johnson & Johnson; Novartis Pharmaceutical Corporation; Pfizer Inc.; Sanofi US; and Samumed, LLC.

³ Public Hearing Notice at 60299.

⁴ Letter from Leslie Kux, Assistant Commissioner for Policy, to Alan R. Bennett, Joan McPhee, Paul Kalb, & Coleen Klasmeier, Docket Nos. FDA-2011-P-0512 and FDA-2013-P-1079, 8 (June 6, 2014).

On January 19, 2017, FDA reopened the comment period for the hearing and unexpectedly issued a memorandum entitled “Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products” (the “Memorandum”). In the Memorandum, FDA acknowledged that stakeholders had testified at the public hearing that “FDA had not sufficiently discussed the First Amendment in the notification of public hearing.”⁵ However, rather than responding directly to stakeholder testimony, the Memorandum merely asserted that First Amendment speech interests are outweighed by the agency’s regulatory and policy interests, and that the agency’s expansive interpretation of its own authority to regulate manufacturer speech is necessary to protect the public health. The Memorandum, moreover, entirely ignored the grave Fifth Amendment issues presented by the lack of clarity in the agency’s regulatory framework.

The same day, FDA issued two draft guidance documents related to the regulation of manufacturer speech: *Drug and Device Manufacturers’ Communications with Payors, Formulary Committees, and Similar Entities—Questions and Answers*, and *Medical Product Communications Consistent with the FDA-Required Labeling—Questions and Answers*. The MIWG supports FDA’s endeavor to provide additional clarity in these two discrete areas and the agency’s recognition of the value of manufacturer communications. Nevertheless, we remain concerned that the agency continues to regulate manufacturer speech through a patchwork of purportedly non-binding draft guidance documents and exceedingly narrow and unclear safe harbors, and has yet to set forth a cohesive framework for regulating manufacturer speech in view of constitutional limitations. Our comments focus on the comprehensive review itself, and particularly on the analytical framework that we believe should inform FDA’s consideration of changes to existing policies governing manufacturer speech.⁶

Our comments are organized into two sections. In Part I, we address the First and Fifth Amendment framework that governs FDA’s regulation of manufacturer communications. In Part II, we analyze certain alternative policies identified during the public hearing, and summarize various proposals that MIWG has advanced over several years to improve FDA’s regulatory framework in view of constitutional and statutory limitations.

⁵ Memorandum at 1; *see also* Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products; Availability of Memorandum; Reopening of the Comment Period, 82 Fed. Reg. 6367, 6368 (Jan. 19, 2017).

⁶ Our comments are not meant to provide an exhaustive analysis of the deficiencies in FDA’s approach to the regulation of manufacturer speech, nor do they propose a comprehensive framework for addressing those deficiencies. Members of the MIWG have made 18 submissions to various FDA dockets since 2008, which collectively provide significantly more detail on issues for the agency to consider as it conducts its comprehensive review. The submissions are available via the MIWG website, www.miwg.org.

I. RECENT FDA PRONOUNCEMENTS HAVE FAILED TO SUBJECT THE AGENCY’S SPEECH RESTRICTIONS TO THE REQUIRED CONSTITUTIONAL SCRUTINY

A. The Notice and Memorandum Did Not Properly Account for the First Amendment Limitations on FDA’s Regulation of Manufacturer Speech

Long-standing Supreme Court doctrine makes clear that the First Amendment protects scientific expression⁷ and commercial speech.⁸ The Supreme Court has held that the government may not “completely suppress the dissemination of concededly truthful information about entirely lawful activity,”⁹ and in 2011 affirmed both that medical product manufacturers’ truthful, non-misleading communications are entitled to First Amendment protection, and that any government restrictions on those communications are accordingly subject to “heightened scrutiny” under the First Amendment.¹⁰ The First Amendment is thus not merely a factor in FDA’s regulatory approach, nor is it merely to be balanced against other agency policy priorities. While FDA may restrict speech where necessary to achieve substantial governmental interests, it must ensure that it is truly necessary to do so. The notice and Memorandum failed to acknowledge these First Amendment commands.

Many of FDA’s statements in connection with the public hearing and in the Memorandum reflected a basic misunderstanding of this constitutional analysis. They suggested that FDA has unbounded authority to determine what truthful, non-misleading speech is valuable to health care professionals (HCPs) and payors, and to decide, as a matter of policy, what speech it will permit. Specifically, the first questions asked in the Federal Register notice announcing the public hearing focused on comparing the “benefits” and “drawbacks or risks” of increased manufacturer communications about unapproved products,¹¹ and then-Commissioner Califf’s introductory remarks at the hearing similarly questioned whether the agency’s public health mission could accommodate increased flexibility in manufacturer communications.¹² The Memorandum further reinforced this view, focusing on the policy justifications for various levels

⁷ *Bd. of Trs. v. Sullivan*, 773 F. Supp. 472, 474 (D.D.C. 1991) (“[T]he First Amendment protects scientific expression and debate just as it protects political and artistic expression.”); *Miller v. California*, 413 U.S. 15, 34 (1973) (The First Amendment protects speech that has “serious . . . scientific value.”).

⁸ *Edenfield v. Fane*, 507 U.S. 761, 767 (1993) (“The commercial marketplace, like other spheres of our social and cultural life, provides a forum where ideas and information flourish.”).

⁹ *Va. State Bd. of Pharm. v. Va. Citizens Consumer Council, Inc.*, 425 U.S. 748, 773 (1976).

¹⁰ *Sorrell v. IMS Health*, 564 U.S. 552 (2011).

¹¹ Public Hearing Notice at 60302.

¹² Transcript of FDA Public Hearing, Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products; Public Hearing; Requests for Comments (Nov. 9, 2016) (“Day One Hearing Transcript”) at 24:10-20 (noting that “firm’s communications about unapproved uses of their approved or cleared products” could compromise “the important public health interests that the FDA premarket review system advances, . . . and patients could be harmed”).

of regulation and describing constitutional limitations as merely one set of considerations that agency officials must “harmonize” or “integrate” with public health interests.¹³

Because the notice and the Memorandum both operated from the flawed assumption that the First Amendment can be subordinated to FDA’s regulatory preferences and policy interests, they did not give sufficient weight to key constitutional limitations. As FDA revises its regulatory framework, the relevant constitutional restraints *must* remain at the forefront.

1. The Notice and Memorandum Did Not Understand that Controlling the Flow of Information Is Not a Permissible Means to Influence Behavior

The hearing notice posed a number of questions about “incentives,”¹⁴ reflecting a view that FDA may restrict the communication of information in order to influence behavior. The notice referred to the nexus between manufacturer speech and prescribing decisions, manufacturer decisions regarding sponsorship of clinical research,¹⁵ and individual decisions regarding whether to participate as a subject in a clinical trial.¹⁶ FDA continued this line of analysis in the Memorandum, indicating that “maintaining incentives for clinical trial participation” and “protecting innovation incentives” are part of “FDA’s larger substantial interest in protecting and promoting public health.”¹⁷

In both documents, FDA fails to acknowledge the fundamental tenet of First Amendment jurisprudence that the government generally may not restrict accurate speech about lawful activity in order to prevent “bad decisions” or to influence people to make choices the

¹³ See, e.g., Memorandum at 1 (“The FD&C Act, its implementing regulations, and FDA policies *must protect the public health*—the fundamental interest underlying FDA’s mission and the statutory framework—*while harmonizing this goal with First Amendment interests* in the dissemination of truthful, accurate, and non-misleading information regarding medical products. . . .”) (emphasis added); see also *id.* at 26 (noting FDA policy must “integrate the complex mix of numerous, and sometimes competing, interests at play”).

¹⁴ E.g., Public Hearing Notice at 60302 (“What information or systems exist to help FDA determine how firms’ increased communication of information about unapproved uses of approved/cleared medical products could affect prescribing as well as medical product development and research into new uses of approved/cleared products? . . . How could firms’ increased communication of information about unapproved uses of approved/cleared medical products affect patient incentives to enroll in clinical trials? Related to this, FDA is interested in information on how firms’ increased communication of this information could impact their incentives to generate robust data to fully assess the risks and benefits of new uses and to apply for FDA marketing authorization for new uses of approved/cleared products.”).

¹⁵ FDA’s current approach, in fact, discourages manufacturers from conducting additional research and generating relevant data that could assist HCPs and payors because the pathway for sharing such information is not clear.

¹⁶ *Id.* at 60301 (asking “how increased communications about unapproved uses would impact incentives to conduct biomedical research submitted for FDA review and subjects’ willingness to participate in such research” and how they “would affect incentives for submission of . . . data to the Agency for marketing authorization.”).

¹⁷ Memorandum at 3.

government prefers.¹⁸ “[T]he general rule is that the speaker and the audience, *not* the government, assess the value of the information presented,”¹⁹ and it is “anathema” to the First Amendment to bar speech based on the “perceived dangers of that knowledge.”²⁰ The Supreme Court has regularly criticized the “paternalistic assumption” underlying government restrictions on communication designed “to prevent members of the public from making bad decisions with the information.”²¹ FDA must clearly recognize that the First Amendment precludes it from restricting manufacturers, and manufacturers alone, from sharing truthful, non-misleading information simply to influence certain behavior.

2. Content- and Speaker-Based Restrictions On Speech Must Be Narrowly Drawn

In *Sorrell*, the Supreme Court made clear that a regulatory framework that disfavors speech with particular content and by “specific speakers, namely pharmaceutical manufacturers,” is subject to heightened scrutiny.²² Just recently, in *Reed v. Gilbert*, the Supreme Court reaffirmed that laws and regulations qualify as speaker- or content-based restrictions, and therefore must be narrowly tailored in order to comply with the First Amendment, if they restrict protected speech because of the identity of the speaker, “the topic discussed, or the idea or message expressed.”²³

The Memorandum acknowledged that FDA’s regulations are content- and speaker-based restrictions on speech, but attempts to avoid searching constitutional review by claiming that “[i]t makes sense for these restrictions to apply only to firms, who have an economic motivation related to product distribution. A broader approach—that, for example, restricted all communication about unapproved uses by both firms and others—would impact more speech and would be less tailored to advancing the various government interests.”²⁴ This attempted justification falls short for a number of reasons.

Mere belief that a speaker-based restriction “makes sense” is insufficient to justify prohibiting truthful, non-misleading communications under the level of scrutiny that the First Amendment requires. The Supreme Court has regularly explained that government agencies may not rely on the identity of the speaker or the content of the message to distinguish between

¹⁸ See, e.g., *Ashcroft v. Free Speech Coalition*, 535 U.S. 234, 253 (2002) (“The mere tendency of speech to encourage unlawful acts is not a sufficient reason for banning it”).

¹⁹ *Va. State Bd. of Pharm.*, 425 U.S. at 767.

²⁰ *44 Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 496-97 (1996) (quoting *Va. State Bd. of Pharm.*, 425 U.S. at 770).

²¹ *Id.*; see also *Rubin v. Coors Brewing Co.*, 514 U.S. 476, 497 (1995) (Stevens, J., concurring); *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 374 (2002).

²² *Sorrell*, 564 U.S. at 564.

²³ 135 S. Ct. 2218, 2227 (2015).

²⁴ Memorandum at 25.

permitted and prohibited speech. Nor does the fact that manufacturers have an economic interest justify singling them out; so too do other speakers, including public and private payors, who remain free to engage in many of the same communications that are prohibited to manufacturers. FDA must ensure that any such speaker- and content-based restrictions are narrowly tailored to satisfy the heightened scrutiny standard imposed by *Sorrell*.²⁵

3. FDA’s Review Must Also Account For Listeners’ First Amendment Rights

The Supreme Court has explained that “[f]reedom of speech presupposes a willing speaker. But where a speaker exists, as is the case here, the protection afforded is to the communication, to its source and to its recipients both.”²⁶ Listeners’ “concern[s] for the free flow of commercial speech often may be far keener than [their] concern[s] for urgent political dialogue,” and these interests are particularly important “in the field of medicine and public health, where information can save lives.”²⁷

The Memorandum presumed that FDA—and FDA alone—is equipped to assess the value of manufacturer speech.²⁸ This paternalistic approach ignored the First Amendment rights of listeners. HCPs and payors testified to this effect at the public hearing, explaining that they are eager to receive additional communications from manufacturers to inform their decision-making and to improve healthcare outcomes, but the Memorandum was virtually silent on this point.²⁹

B. The Memorandum Improperly Minimized the Impact of Recent Court Decisions

Recent federal court decisions, which recognize the First Amendment protection afforded truthful, non-misleading speech about unapproved uses, are firmly rooted in the constitutional principles described *supra*. The Memorandum incorrectly attempted to diminish the impact of

²⁵ *Sorrell*, 564 U.S. at 571.

²⁶ *Va. State Bd. of Pharm.*, 425 U.S. at 756.

²⁷ *Sorrell*, 564 U.S. at 566 (internal quotations omitted).

²⁸ *E.g.*, Memorandum at 19 (explaining the importance of FDA review by arguing that “the ability to adequately assess benefit and risk from an unapproved use is dramatically impacted by the objective and transparent presentation of data and information”).

²⁹ *See* Day One Hearing Transcript at 276:13-19 (Dr. William Welch of the American Association of Neurological Surgeons/Congress of Neurological Surgeons testified that, “as a group, [neurosurgeons] support the dissemination of scientifically valid information between healthcare professionals and manufacturers” and “urge the FDA to allow industry and others to provide physicians with access to such clinical information”); Transcript of FDA Public Hearing, Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products; Public Hearing; Requests for Comments (Nov. 10, 2016) (“Day Two Hearing Transcript”) at 206:22-207:6 (Dr. Doyle Stulting of the American Society for Cataract and Refractive Surgery testified that “FDA’s current regulations unnecessarily . . . interfere with the dissemination of scientifically valid information between healthcare professionals and manufacturers,” which “ultimately denies physicians access to vital current real world experiences and adversely affects healthcare outcomes”).

these significant decisions, and did so both by presenting inaccurate arguments to justify FDA’s overly restrictive regulatory framework and by mischaracterizing the public health benefits of truthful, non-misleading manufacturer communications.

1. Numerous Cases Make Clear that Truthful, Non-Misleading Speech is Entitled to Robust First Amendment Protection

The Memorandum criticized and sought to limit the significance of the Second Circuit’s recent decision in *United States v. Caronia*³⁰ on the ground that “the panel majority” conducted a deficient *Central Hudson* analysis that did not “evaluat[e] FDA’s implementation approach” or “consider multiple components of public health interests advanced by” that approach.³¹ The Memorandum also sought to diminish the impact of *Amarin Pharma, Inc. v. FDA*,³² describing its holding as limited to the Second Circuit.³³ But the Memorandum missed the mark. *Caronia* and *Amarin* are not outliers, and each applied well-grounded, bedrock constitutional principles.

In *Caronia*, the Second Circuit held that the First Amendment protects “the ability of physicians and patients to receive potentially relevant treatment information” from manufacturers, which would in turn encourage more “informed and intelligent treatment decisions.”³⁴ The court stressed that, because off-label use is a “lawful activity” and speech about it is not inherently “false or misleading,”³⁵ FDA could not “‘paternalistically’ interfere[] with” such communication.³⁶ The Second Circuit also explained that speech “‘in aid of pharmaceutical marketing’” is entitled to First Amendment protection under *Sorrell*, and is therefore subject to narrow tailoring requirements.³⁷ Three years later, the court in *Amarin* confirmed the applicability of these principles to “truthful and non-misleading speech promoting the off-label use of an FDA-approved drug.”³⁸

Although the Memorandum attempted to dismiss these cases as outliers, they apply well established principles. The *Caronia* court, for example, alternatively analyzed FDA’s regulations under the long-standing four-part *Central Hudson* test.³⁹ The *Central Hudson* test

³⁰ 703 F.3d 149, 166 (2d Cir. 2012).

³¹ Memorandum at 23.

³² 119 F. Supp. 3d 196, 226 (S.D.N.Y. 2015).

³³ Memorandum at 22.

³⁴ *Caronia*, 703 F.3d at 164.

³⁵ *Id.* at 165.

³⁶ *Id.* at 166-67.

³⁷ *Id.* at 161-62 (citing *Sorrell*, 564 U.S. at 557).

³⁸ *Amarin*, 119 F. Supp. 3d at 226 (emphasis in original).

³⁹ *Central Hudson Gas & Elec. Corp. v. Pub. Serv. Comm’n*, 447 U.S. 557 (1980).

was preceded by *Virginia State Board of Pharmacy v. Virginia Consumer Council*, where the Supreme Court recognized that society has “a strong interest in the free flow of commercial information” and held that the government cannot suppress truthful, non-misleading commercial speech simply out of fear of the effect it may have on listeners.⁴⁰ In *Edenfield v. Fane*, the Court explained accordingly that “the general rule is that the speaker and the audience, not the government, assess the value of the information presented.”⁴¹ The Supreme Court further noted the high bar the government faces when it seeks to regulate speech in *44 Liquormart, Inc. v. Rhode Island*, explaining that the “First Amendment directs us to be especially skeptical of . . . bans against truthful, nonmisleading commercial speech” because they “rarely seek to protect consumers from either deception or overreaching” and instead generally “seek to keep people in the dark for what the government perceives to be their own good.”⁴² In *Thompson v. Western States Medical Center*, the Supreme Court similarly “rejected the notion that the Government has an interest in preventing the dissemination of truthful commercial information in order to prevent members of the public from making bad decisions with the information.”⁴³ And, most recently, the Supreme Court unequivocally held in *Sorrell* that “[s]peech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment” and therefore restrictions on that speech “must be subjected to heightened judicial scrutiny.”⁴⁴

FDA must recognize the long-standing and central First Amendment principles that animated *Caronia* and *Amarin*. Indeed, what is most notable in the Memorandum is its failure to refine FDA’s approach to manufacturer speech in light of the important constitutional interests at stake.

2. The Memorandum Understated the Public Health Value of Truthful, Non-Misleading Communications

a. Truthful, Non-Misleading Manufacturer Communications Further the Public Health

FDA has long recognized that off-label prescribing is a central feature of patient care. For example, a senior FDA official submitted a Declaration in the *Amarin* litigation acknowledging that prohibiting off-label use would, in her words, “substantially restrict the discretion and independence of healthcare providers, and would fail to take into account the interests behind allowing healthcare providers to determine the best treatment options for individual patients in specific circumstances.”⁴⁵ Recognizing the importance of off-label

⁴⁰ 425 U.S. at 764, 773.

⁴¹ 507 U.S. at 767.

⁴² 517 U.S. at 503.

⁴³ 535 U.S. at 374.

⁴⁴ 564 U.S. at 557.

⁴⁵ Declaration of Janet Woodcock, *Amarin Pharma, Inc. v. FDA*, No. 1:15-cv-03588-PAE (Jul. 7, 2015) (Dkt. 52 at 43).

prescribing, FDA has repeatedly underscored the critical need for accurate *information* about off-label uses. Put another way, FDA acknowledges that, in the absence of approved prescribing information to support an off-label use, there is a need for truthful, non-misleading, clinically relevant information to assist prescribers in making well-informed treatment decisions. As far back as 1972, FDA acknowledged that, once a product is on the market, physicians are “responsible for making the final judgment as to which, if any, of the available drugs patients will receive in light of the information contained in their labeling *and* other adequate scientific data available.”⁴⁶ The dissemination of up-to-date medical information about a product—irrespective of the information in the product’s labeling—helps to guide treatment decisions and ensures that patients receive care based on current, sound, scientific and clinical information.⁴⁷

Numerous stakeholders embraced this viewpoint at the public hearing, with both physicians and payors speaking to explain the clinical and economic value of off-label and out-of-label information,⁴⁸ and FDA reiterated in the Memorandum that HCPs “may be interested in information about unapproved uses of products, and payors and similar entities have also expressed interest in information that is potentially relevant to coverage decisions which affect patient care.”⁴⁹ This information is particularly valuable when treating rare conditions, or working in fields like oncology where clinical practices are rapidly evolving. Additionally, when providing truthful and non-misleading information about off-label uses, manufacturers can identify potential harmful or inappropriate uses and, in communicating about uses for which there is scientific evidence of efficacy, provide sufficient information so that HCPs may prescribe or use the products safely.

⁴⁶ Legal Status of Approved Labeling for Prescription Drugs, 37 Fed. Reg. 16503, 16504 (Aug. 15, 1972) (emphasis added).

⁴⁷ For example, the Associate Commissioner for Health Affairs at FDA wrote in 1992 that “the very latest information that can be of value to physicians . . . must be made available as soon as possible. Frequently, unlabeled use information is extremely important.” Stuart Nightingale, *Unlabeled Uses of Approved Drugs*, 26 Drug Info. J. 141, 145 (1992).

⁴⁸ See, e.g., Day One Hearing Transcript at 281:20-282:2 (Dr. Welch testified that using medical products “in an off label or physician directed application” can be part of a physician’s “moral and ethical duty to provide the best possible treatment for the patient”); Day Two Hearing Transcript at 207:18-208:2 (Dr. Stulting testified that “[o]ff-label use of drugs and devices is actually very common in my practice and, indeed, the practice of medicine” and explained that “failure to prescribe medications or use devices off-label would quickly place many of us, including me, at risk for a malpractice lawsuit”). Payor testimony included the remarks of Dr. Samuel Nussbaum of Anthem, Inc., Mr. Douglas Stoss of Humana, and Dr. Megan Coder of the Pharmaceutical Care Management Association. See Day One Hearing Transcript at 192:8-11 (Dr. Nussbaum testified and explained the benefits of allowing “pharmaceutical companies [to] speak openly with health plans about drugs going through the FDA approval process, particularly with regard to product efficacy, safety, and pharmacoeconomic information”); *id.* at 200:14-18 (Stoss explained that “it is more important than ever that payors be able to talk to manufacturers about on label and off label indications, as well as pricing and projected utilization”); Day Two Hearing Transcript at 275:1-5 (Dr. Coder testified that “[i]ncreased data sharing” between manufacturers and interested parties “will allow payors and PBM’s to identify appropriate treatment options for patients while better preventing unintended harm and injury”).

⁴⁹ Memorandum at 17.

Despite FDA’s repeated acknowledgements that off-label use is vital to the public health, and that the provision of truthful and non-misleading information is necessary in many cases to support safe and appropriate prescribing practices, the agency attempted in the Memorandum to justify overly broad restrictions on manufacturer speech by focusing on the harms associated with off-label communications regarding products that are not approved at all for sale as drugs, and on communications that are false, not properly supported by scientific evidence, or otherwise misleading.⁵⁰

To be clear, the members of MIWG support safe and appropriate use of their products and do not seek to convey information that is false or misleading. Nor has MIWG asserted that manufacturers have the unfettered ability to make efficacy claims for new uses without prior FDA approval. But FDA’s speech restrictions limit far more than that, and FDA’s notice and Memorandum did not reflect the searching constitutional inquiry that is required. Moreover, they defended a broad interpretation of the agency’s authority that does not distinguish among the myriad specific speech restrictions that have been established under the statute and require individualized assessments.⁵¹ While the First Amendment analysis may differ according to the precise type of speech at issue, the Memorandum did not recognize or account for any such differences, instead invoking the public health and safety in talismanic fashion.

b. The Canadian Study Does Not Support Restrictions on Manufacturer Speech

At the public hearing and in the Memorandum, FDA relied heavily on a Canadian study⁵² “show[ing] an association between unapproved uses and adverse drug events”⁵³ to assert that the agency’s approach to restricting manufacturer speech is both necessary to protect the public health and permissible under the First Amendment. However, the Canadian study assessed the impact of off-label *use*, not off-label *communications*, and the study’s relevance to questions about whether to restrict *communications* is limited to its affirmative demonstration of the value of additional information sharing. Furthermore, with regard to off-label use, the Canadian study has significant limitations and does not support the notion that off-label use is generally harmful, lacking in substantiation, or inherently riskier than on-label uses. As a consequence, the Canadian study cannot be used to justify the status quo, and indeed would support FDA action to refine its regulation of manufacturer speech in light of First Amendment principles.

The Canadian study does not support a general assertion that speech restrictions are necessary to protect against harms associated with off-label use, and in fact demonstrates that

⁵⁰ See, e.g., *id.* at 6-7, 13, 18-19, 23.

⁵¹ To offer one of many possible examples, FDA for many years has interpreted its regulations to prohibit a company from making comparative claims with respect to a use for which a drug has already been approved. See, e.g., 21 C.F.R. § 22.1(e)(6)(i)-(ii). While MIWG welcomes the recent draft guidance in this area, FDA’s regulations currently reflect the agency’s historic position and should be amended to reflect FDA’s updated thinking.

⁵² Tewodros Eguale, MD, PhD et al., Association of Off-Label Drug Use and Adverse Drug Events in an Adult Population, 176 JAMA INTERN. MED. 55 (Nov. 2, 2015) [hereinafter “Canadian Study”].

⁵³ Memorandum at 24.

greater information sharing would benefit the public health. The study examined adverse drug events associated with off-label uses of prescription drugs by analyzing the electronic health records of 46,021 patients in primary clinics in Quebec. While the study concluded that *all* off-label drug use is a risk factor for adverse drug events,⁵⁴ it in fact found that only off-label use *lacking in strong scientific evidence*⁵⁵ was associated with a higher rate of adverse drug events compared with on-label use of prescription medications.⁵⁶ Importantly, the Canadian study also found that off-label use that *was supported* by strong scientific evidence was associated with the *same* risk of adverse drug events as on-label use.⁵⁷

While several speakers at the public hearing⁵⁸ cited the authors' conclusions to support restrictions on manufacturer speech concerning off-label use, the study actually underscores the importance of providing information to HCPs regarding scientifically supported off-label uses. As the authors of the Canadian study explained, adverse drug events were more likely to occur when medications were prescribed off-label because the labeling information available about safe dose ranges and contraindications was inadequate, an issue that could be addressed by providing supplemental safety information.⁵⁹ The authors also noted the difficulty that HCPs have in "keep[ing] up with rapidly changing medical information," further highlighting the importance of their receiving accurate information to support prescribing decisions.⁶⁰

Furthermore, the Canadian study did not analyze any positive outcomes that were associated with either on- or off-label use of the medications studied, and did not measure the severity of the adverse events reported. The rate of adverse drug events cited in the Canadian

⁵⁴ Canadian Study at 61-62.

⁵⁵ Strong scientific evidence exists, according to the authors, when "(1) the drug is effective or favors efficacy for the off-label treatment indication, (2) the drug is recommended for at least most patients with the off-label treatment indication, and (3) the studies used to evaluate efficacy and the strength of evidence include at least [one] randomized controlled trial." *Id.* at 56-57.

⁵⁶ *Id.* at 55 (emphasis added).

⁵⁷ *Id.* at 56-57.

⁵⁸ *See, e.g.*, Day One Hearing Transcript at 324:18-328:17 (Dr. Sidney Wolfe of Public Citizen's Health Research Group testified, "The next study . . . had some definitions of what it would require to have strong evidence. One was that a study, at least one randomized controlled study would show that it is effective for the off label use, or favors effectiveness . . . So beyond lacking strong evidence of effectiveness, more than a 50 percent, adjusted for all the confounders, increase in adverse drug reactions compare to on label use . . . [O]ff label use, and particularly off label use without strong scientific evidence, is a risk factor for adverse drug events"); Day Two Hearing Transcript at 191:20-192:2 (Dr. Adriane Fugh-Berman of the Georgetown University Medical Center testified, "Off-label use increases adverse events. Dr. Wolfe cited a Canadian study yesterday that found that off--that adverse effects were higher for off-label use than on-label use. And for uses that had no scientific support, it was even higher"); *id.* at 15:21-16:1 (Dr. Joshua Sharfstein of the Johns Hopkins Bloomberg School of Public Health testified, "There's recently a study at the population level showing how there's significant increase in adverse drug events for unproven, off-label uses").

⁵⁹ Canadian Study at 60.

⁶⁰ *Id.*

study does not, therefore, account for the favorable risk-benefit ratio of the off-label use in particular patients.⁶¹ Many other studies, moreover, reflect the value of off-label use. In a recent study of off-label use of antibiotic prescriptions in a tertiary hospital in France, for example, the researchers found that 78.9% of off-label uses were prescribed in accordance with guidelines on infectious diseases, and that the rate of reported adverse events between patients who were prescribed antibiotics on-label and those who were prescribed antibiotics off-label was not statistically different.⁶² Another study of off-label use of chemotherapy regimens in older women with breast cancer concluded that 64% of off-label use was supported by established oncology guidelines.⁶³ A different study of off-label use of cancer therapies in women of all ages with breast cancer similarly concluded that “most off-label encounters were evidence-based” as characterized by evidence from one or more well-designed randomized controlled trials.⁶⁴

Moreover, as the decision in *Caronia* makes clear, courts will not reflexively defer to FDA’s assertions, and any suggestion that the Canadian study will sustain any and all restrictions on manufacturer speech under either *Central Hudson* or *Sorrell*’s “heightened scrutiny” standard is therefore without foundation. The government fully briefed the public health argument in *Caronia*, asserting that “restricting the promotion of off-label uses by manufacturers and their representatives directly advances the compelling governmental interest in drug safety and public health” and that any limitation on FDA’s ability to restrict off-label communications would cause FDA’s “regulatory machinery for protecting patients from unsafe and ineffective drugs” to be “drastically impaired.”⁶⁵ The Second Circuit considered this argument and acknowledged that “the government’s asserted interests in drug safety and public health,” including its “interest in preserving the effectiveness and integrity of the FDCA’s drug approval process,” are “substantial.”⁶⁶ Nevertheless, the court also found that “[t]he government ha[d] not established a ‘reasonable fit’ among its interests in drug safety and public health” and “the lawfulness of off-label use,”⁶⁷ including as recognized by other agencies and branches within the Department of

⁶¹ Additionally, the study provides little information about the condition of the patients who were prescribed drugs, the diseases that were treated off-label, whether alternative therapies were available, and what the consequences would have been if the patients did not receive treatment.

⁶² Benjamin Davido et al., *High Rates of Off-Label Use in Antibiotic Prescriptions in a Context of Dramatic Resistance Increase: A Prospective Study in a Tertiary Hospital*, 47 INT’L J. OF ANTIMICROBIAL AGENTS 490 (2016).

⁶³ Anne A. Eaton, Camelia S. Sima, and Katherine S. Panageas, *Prevalence and Safety of Off-Label Use of Chemotherapeutic Agents in Older Patients With Breast Cancer: Estimates From SEER-Medicare Data*, 14.1 J. NAT’L COMPREHENSIVE CANCER NETWORK, 57 (2016).

⁶⁴ Sophie Hamel et al., *Off-Label Use of Cancer Therapies in Women Diagnosed with Breast Cancer in the United States*, 4:209 SPRINGERPLUS 1, 8 (2015).

⁶⁵ Br. of United States, *United States v. Caronia*, 703 F.3d 149 (2d. Cir. 2012), Nos. 09-5006-cr(L), 10-0750(CON), 2010 WL 6351497 (C.A.2), at *59, 61-62.

⁶⁶ *Caronia*, 703 F.3d at 166.

⁶⁷ *Id.* at 168.

Health and Human Services.⁶⁸ While the Second Circuit was clear that its conclusion was “limited to FDA-approved drugs for which off-label use is not prohibited,” and that it did not hold “that the FDA cannot regulate the marketing of prescription drugs,” it was also clear that the government must advance its legitimate interests through “limited and targeted regulations on speech.”⁶⁹ Thus, the Canadian study does not resolve the inconsistency in the government’s own approach to off-label use, and does not address the defect the Second Circuit identified in the regulatory scheme.

C. The Notice and Memorandum Failed To Address Important Fifth Amendment Issues

The Fifth Amendment requires precise, clear rules that provide regulated industry with “fair notice of what is prohibited.”⁷⁰ Due Process principles apply with “special force” where, as here, government regulations implicate the First Amendment.⁷¹ “[R]igorous adherence to [notice] requirements is necessary to ensure that ambiguity does not chill protected speech,”⁷² and vague and overbroad government regulations are “particularly treacherous” where the threat of criminal penalties “may deter those who seek to exercise protected First Amendment rights.”⁷³

FDA’s regulatory framework does not clearly define the boundaries between permissible and impermissible communications and is otherwise rife with undefined terms and ambiguities. Members of the MIWG have repeatedly raised Fifth Amendment concerns and have provided in our citizen petitions and public comments to draft FDA guidance documents several examples of the ways in which the agency’s regulation of manufacturer communications is constitutionally deficient. Those deficiencies are due in part to the agency’s practice of regulating manufacturer speech through non-binding draft guidance documents, *ad hoc* warning and untitled letters, and advisory comments that are not publicly available, none of which incorporates public input or set forth unifying, cohesive principles for manufacturers to consider when evaluating proposed

⁶⁸ For example, the Medicare Benefits Policy Manual specifically provides that “FDA approved drugs used for indications other than what is indicated on the official label may be covered under Medicare,” and Medicare may reimburse off-label drug uses, “taking into consideration the major drug compendia, authoritative medical literature and/or accepted standards of medical practice.” Medicare Benefits Policy Manual, Ch. 15, § 50.4.2. Similarly, the Department of Veterans Affairs provides for off-label use of medications “if it is determined by appropriate healthcare professionals that the care is needed to promote, preserve, or restore the health of the individual and is in accord with generally accepted standards of medical practice.” 38 C.F.R. § 17.38(b).

⁶⁹ *Caronia*, 703 F.3d at 168-69.

⁷⁰ *FCC v. Fox Television Stations, Inc.*, 132 S. Ct. 2307, 2318 (2012) (*Fox II*) (quoting *United States v. Williams*, 553 U.S. 285, 304 (2008)).

⁷¹ *Reno v. ACLU*, 521 U.S. 844, 874 (1997).

⁷² *Fox II*, at 2317; see also *Keyshian v. Bd. of Regents of the U. of N.Y.*, 385 U.S. 589, 604 (1967) (noting that “standards of permissible statutory vagueness are strict in the area of free expression . . . Because the First Amendment freedoms need breathing space to survive, government may regulate in the area only with narrow specificity”) (quoting *NAACP v. Button*, 371 U.S. 415, 438 (1963)).

⁷³ *Buckley v. Valeo*, 424 U.S. 1, 76-77 (1976).

communications. And although FDA attempts to defend its sweeping speech restrictions on manufacturer communications by pointing to various “safe harbors” for off- and out-of-label communications that it has established over the years, those “safe harbors” do not remedy the constitutional defects inherent in the regulatory framework because they are narrow, ambiguous, and unreliable given FDA’s discretion to change them and their lack of binding effect on the Department of Justice, or other enforcement authorities at the federal and state level.

FDA’s recent draft guidance on communications consistent with the FDA-required labeling is illustrative of the Fifth Amendment issues raised by the lack of clear, binding rules. While the draft guidance takes important steps toward allowing manufacturers greater flexibility to convey truthful, non-misleading information based on differing degrees of substantiation, FDA fails to address the relationship between this guidance and an FDA regulation requiring substantial evidence for promotional claims made in advertising.⁷⁴ Because DOJ is not obligated to follow non-binding FDA guidance, and there is no codification of the flexibility afforded in the draft guidance, FDA’s failure to amend the regulation may leave manufacturers at risk when sharing truthful, non-misleading information.⁷⁵

In conducting its comprehensive review, the agency has not clearly acknowledged the Fifth Amendment Due Process concerns raised by the current scheme. Nor has FDA addressed those concerns by issuing clear, binding regulations. FDA’s failure to do so inhibits the dissemination of accurate information that is clinically valuable. Furthermore, so long as FDA continues to regulate truthful, non-misleading manufacturer speech through non-binding draft guidance documents and *ad hoc* warning and untitled letters, certain of its practices will raise serious First and Fifth Amendment concerns.

II. FDA SHOULD CONSIDER REGULATORY ALTERNATIVES THAT ADDRESS CONSTITUTIONAL FLAWS IN THE CURRENT REGIME AND SAFEGUARD THE PUBLIC HEALTH BENEFITS OF SHARING ADDITIONAL INFORMATION

A. Manufacturers’ Right To Communicate Accurate Information Should Not Be Conditioned On Peer Review Or Data Disclosure Requirements

There is evidence that FDA is considering adopting a policy of permitting manufacturers to communicate in truthful, non-misleading ways about their products only if they also satisfy certain requirements intended to address concerns about potential bias. On June 7, 2016, then-FDA Commissioner Dr. Robert Califf participated at the Biotechnology Innovation Organization (BIO) International Convention in San Francisco, and said the following about manufacturer communications:

⁷⁴ 21 C.F.R. § 202.1(e)(6).

⁷⁵ The absence of clear, binding rules also impairs innovation. For startup companies with limited resources, regulatory uncertainty and the potential for criminal sanctions can pose substantial—even existential—risks. For example, this uncertainty can lead to inefficient program design or market avoidance, both of which can harm innovation.

“My personal view is that companies controlling that information is not the ideal. . . .”

“If it’s publicly available, professional groups can analyze that information fairly easily. If you take the FDA label and a clinical practice guideline for the disease, you’ve pretty much got the playbook for how people should think about it.”

“. . . I’ve not looked to industry to be the least biased source of information. So to the extent that industry has information, it’s definitely my goal to get it out there. I just want to make every effort to have it go through the channels that don’t have bias.”⁷⁶

Similarly, at the hearing, Dr. Califf expressed concern that manufacturer speech is typically based on non-public data, ostensibly making it inherently less trustworthy than data derived from more “transparent” sources.⁷⁷ He encouraged manufacturers to submit their data for peer review as a condition of sharing them with external constituencies, such as prescribers.⁷⁸ Dr. Califf also mentioned several times during the hearing the recent final rule concerning ClinicalTrials.gov as an example of “increasing transparency” by making information concerning clinical trials publicly available.⁷⁹

These prior comments reflecting support for potential additional requirements for manufacturer dissemination of clinical data appear to rest on flawed assumptions that: (1) manufacturers have little to contribute to knowledge about drug or medical device use because FDA-authorized labeling and clinical practice guidelines provide complete information; (2) non-public information should not be disseminated by manufacturers because it cannot be evaluated by professional groups or other third parties; and (3) industry is inherently biased and manufacturers should be required to go through alternative “channels” (*e.g.*, peer review) to communicate about their products. Each of these flawed assumptions is addressed below.

⁷⁶ Robert Califf, Former Commissioner, Food & Drug Admin., Remarks at BIO 2016 International Convention (June 7, 2016), <https://www.youtube.com/watch?v=Q4XCo-FoB7s>.

⁷⁷ See Day One Hearing Transcript at 50:11-18 (“I just want to be clear that we understand what you’re saying . . . you’re suggesting another pathway would be for a company to basically keep the information to itself and promote it without going through those steps of peer review, and with that some people might regard as not being transparent with the information”).

⁷⁸ *Id.* at 65:4-7 (“Are you proposing that there should be no requirement for peer review? That the company could go directly to physicians for example with the results of observational studies[?]”); *id.* at 90:10-15, 91:2-8 (“Dr. Califf [to Coleen Klasmeier, MIWG]: I fully accept peer review has many flaws. How do you feel about non-transparent transmission of information from one person to another, versus full transparency of making it available to the public? Ms. Klasmeier: . . . [O]ur positions have always been based on the idea that the informational needs of this evolving system can and should be satisfied by providing scientific data and analysis of the type that . . . enables prescribers and population-level decision makers to reach their own conclusions.”).

⁷⁹ See, *e.g.*, *id.* at 25:22-26:3.

1. Official Labeling and Clinical Practice Guidelines Do Not Provide Complete Product Information, and Manufacturers Have Access To Information That Is Not Available From Any Other Source

While a product’s labeling contains information about the use for which the product has been studied and found to be “safe and effective,” FDA has long recognized that “the labeling of a marketed drug does not always contain all the most current information available to physicians relating to the proper use of the drug in good medical practice.”⁸⁰ Accordingly, more than forty years ago, FDA established, as a matter of agency policy, that prescriber decisions with respect to drug use are properly informed by information beyond official labeling:

As the law now stands . . . , the Food and Drug Administration is charged with the responsibility for judging the safety and effectiveness of drugs and the truthfulness of their labeling. The physician is then responsible for making the final judgment as to which, if any, of the available drugs his patient will receive in the light of the information contained in their labeling and other adequate scientific data available to him.⁸¹

FDA has incorporated this foundational principle—that prescribing decisions should be based on high-quality out-of-labeling information—in guidance directed to clinical investigators. According to that guidance, marketed drug products should be used “according to the[] best knowledge and judgement [sic]” of physicians as part of good medical practice.⁸² The same is true for both on- and off-label uses: “If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects.”⁸³ Many sources of “adequate,” “firm,” and “sound” evidence supporting clinical decisions are available for reference by prescribers. Not only clinical decision-making, but also utilization management determinations at the population level by payors, integrated delivery systems and networks, and managed care organizations, are premised on a heterogeneous mix of information from a wide range of sources.

Clinical practice guidelines (CPGs) are important, but limited. CPGs rely on a combination of data analysis and consensus to aid physicians in bridging from the clinical investigation to the risk-benefit ratio and likelihood of treatment success in a specific practice scenario. But many clinical situations and products are not governed by any CPG. Moreover, FDA’s current policy for the dissemination of CPGs by manufacturers is not sufficiently flexible

⁸⁰ Labeling for Prescription Drugs Used in Man, 40 Fed. Reg. 15392, 15394 (Apr. 7, 1975).

⁸¹ Notice of Proposed Rulemaking, Legal Status of Approved Labeling for Prescription Drugs; Prescribing For Uses Unapproved By The Food and Drug Administration, 37 Fed. Reg. 16503, 16504 (Aug. 15, 1972).

⁸² FDA, “Off-Label” and Investigational Use of Marketed Drugs, Biologics, and Medical Devices—Information Sheet (last updated Jan. 25, 2016), available at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm>.

⁸³ *Id.*

to facilitate the communication of these materials.⁸⁴ Likewise, approved labeling does not always contain the most up-to-date information about the use of a medical product. For physicians to use their “best knowledge and judgment” in the use of medical products, they must have access to information beyond the FDA-required labeling and CPGs.

Manufacturers often have both unique access to important information and the ability and incentive to distribute it. Manufacturers are typically the single best sources of information about their own products, as the Supreme Court has recognized.⁸⁵ Indeed, the same understanding is reflected in FDA’s regulatory scheme, which imposes on manufacturers—and manufacturers alone—the responsibility to collect, and submit to FDA, information about investigation of, and clinical experience with, their products. Rather than enabling manufacturers to share that truthful, non-misleading information, however, FDA expects HCPs to familiarize themselves with up-to-date treatment information by seeking it out on their own, or by reviewing limited reprints that manufacturers are permitted to disseminate to HCPs (but not to freely discuss with them in most instances). Manufacturers should be permitted to share truthful and non-misleading information proactively to ensure that HCPs may make informed treatment decisions.⁸⁶

2. Much Manufacturer Information Will Never Be Conveyed Through Existing Channels

FDA cannot prohibit manufacturers from communicating beyond approved labeling based on the premise that sufficient alternative channels exist for third parties, which are believed by FDA to be less prone to bias, to provide HCPs, payors, and others with access to the same information. Despite their value, these alternative channels suffer from their own biases and limitations, and would restrict HCPs’ access to valuable information that can improve the public health.

⁸⁴ Comments, Draft Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices, Docket No. FDA-2008-D-0053, at 16 (May 2, 2014) (discussing revised draft guidance that would permit manufacturers to distribute clinical practice guidelines only if they satisfy Institute of Medicine standards of “trustworthiness,” which would eliminate many guidelines of high quality); *see also* Bradley N. Reames, *et al.*, Clinical Evaluation of Oncology Clinical Practice Guidelines, 31 J. OF CLIN. ONCOLOGY 2563, 2563-65 (2013) (reviewing 169 guidelines relating to the four leading causes of cancer mortality in the United States, and concluding that not a single one met the IOM standard).

⁸⁵ *Wyeth v. Levine*, 555 U.S. 555, 578-79 (2009) (“Manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge.”).

⁸⁶ At the hearing, Dr. Andrew Koenig of Pfizer provided specific examples of the types of information that manufacturers develop and wish to share with prescribers, including both new analyses of existing data and prospective data from an active control arm of a pivotal clinical trial that was not included in the drug’s labeling. *See* Day One Hearing Transcript at 119:7-121:10, 121:20-122:8. As Dr. Koenig explained, Pfizer felt constrained in sharing the active control arm data from a particular trial that supported the approval of a drug, so the company’s initial communications about the trial were disseminated without disclosing the results of the active control arm. However, that led HCPs to question why the company was not sharing the complete results of the study. *See id.* at 122:9-13.

a. Peer-Reviewed Publications

MIWG agrees with FDA that peer-reviewed journals provide a valuable avenue for the publication and dissemination of scientific and medical information, and its members routinely rely on the peer review process to share research and other valuable information. Peer review should not, however, be a condition precedent to data sharing. Despite their value, peer-reviewed journals have publication biases that are not always aligned with the goal of providing full and transparent data about a particular product. In addition, publication embargoes involved in peer-reviewed publication can create months-long delays before manufacturers—or indeed, any authors—can meaningfully discuss the findings of their own research.

(i) Publication Bias

There is no guarantee that peer-reviewed journals will accept and publish the full range of data relevant to a particular product. Journals' own statistical analyses show biases influencing which manuscripts are accepted for publication.⁸⁷ As one researcher has put it, “editors have little interest in publishing data that refute, or do not reproduce, previously published work.”⁸⁸ A variety of reasons have been cited to explain this bias, but perhaps the most simple is basic economics. Journals must sell subscriptions, and manuscript selection and publication can be driven as much—or more—by newsworthiness as by scientific rigor. One analysis showed that “an intangible ‘originality’ (‘newsworthiness’) factor and positive outcome were more strongly associated with acceptance than traditional measures of scientific quality.”⁸⁹

(ii) Delays in Data Dissemination

Submission of a study to a peer-reviewed journal requires the submitting party to abide by the publication guidelines of the journal. While many of these guidelines are useful, some journal guidelines restrict the dissemination of any of the study findings prior to publication. Stakeholders both inside and outside FDA have long recognized that patient and physician interests are ill-served by medical journal embargo policies, given the sheer length of time from submission to publication.⁹⁰

If these restrictions were imposed on all forms of manufacturer data, they would have the effect of preventing manufacturers and others from discussing clinically relevant information

⁸⁷ Michael L. Callahan, *et al.*, Positive Outcome Bias and Other Limitations in the Outcome of Research Abstracts Submitted to a Scientific Meeting, 280 JAMA 254 (1998).

⁸⁸ Ulrich Dirnagl, *et al.*, Fighting Publication Bias: Introducing the Negative Results Section, 30 J. CEREB. BLOOD FLOW METAB. 1263 (2010).

⁸⁹ *Id.* at 1263.

⁹⁰ Scott Gottlieb, MD, Speech before 2006 Clinical Research Educational Conference (May 18, 2006), available at <http://www.fda.gov/NewsEvents/Speeches/ucm051955.htm> (“[E]ditors of major journals have espoused greater transparency in the clinical research system, . . . [b]ut journals . . . have enhanced the value of their franchises by maintaining very strict embargo policies, and long publishing cycles, that can bottle up clinical results for months and in rare cases years”).

first during the peer review process, and then while a final reviewed manuscript awaits publication. Even following publication of a study to a journal’s subscribers, dissemination of the study findings more broadly may be further limited for a year or more. FDA’s own internal policies concerning public access to FDA-funded research allow journals to restrict access for up to a year.⁹¹

3. It Is Not Enough To Permit Manufacturer Dissemination Of Data Through ClinicalTrials.gov

ClinicalTrials.gov is a highly limited mechanism, in that it can make publicly available certain information about one specific source of information—“clinical trials.” These are limited to studies in which human subjects are “prospectively assigned, according to a protocol, to one or more interventions (or no intervention) to evaluate the effects of the interventions on biomedical or health-related outcomes.”⁹² Many important data sources do not involve prospective assignment, and many sources of information relevant to clinical and utilization decisions in the current healthcare system do not involve trials or studies at all.

For example, the definition of a “clinical trial” in the final rule excludes observational studies; clinical trials are defined only as prospective, interventional studies.⁹³ According to the final rule, observational studies include “prospective cohort studies in which individuals received interventions as part of their medical care, after which the investigator studies prespecified outcomes to examine the impact of those interventions.”⁹⁴ Observational studies also include “retrospective reviews of patient medical records or relevant literature.”⁹⁵

Manufacturers could (and do) voluntarily disseminate information about observational studies, and potentially other sources of data and analysis, using ClinicalTrials.gov. The registry fields on the website would allow for a party to register such studies even if they are not required to do so under the regulations.⁹⁶ But the site allows only the submission of specific pre-identified data fields in tabular format.⁹⁷ Additionally, the platform is a poor vehicle for the presentation of

⁹¹ See FDA, Staff Manual Guide 2126.4 – Access to Results of FDA-Funded Scientific Research (Dec. 29, 2015).

⁹² Clinical Trials Registration and Results Information Submission, 81 Fed. Reg. 64982, 65017 (Sept. 21, 2016) (Under § 11.10(a) “a clinical investigation or a clinical study in which human subjects are prospectively assigned, according to a protocol, to one or more interventions (or no intervention) to evaluate the effects of the interventions on biomedical or health-related outcomes.”).

⁹³ *Id.* at 65017.

⁹⁴ *Id.* at 65023.

⁹⁵ *Id.*

⁹⁶ *Id.* at 65017 (“We note that the ClinicalTrials.gov system allows for the reporting of studies that are not subject to (or are independent of) requirements under section 402(j) of the PHS Act, including under different timelines and with additional information, which means that reporting in these other contexts is not impeded.”).

⁹⁷ *Id.* at 64983.

data from observational studies⁹⁸ and does not provide manufacturers with a useful means of disseminating health care economic information, which is analytical in nature and does not lend itself to presentation using the templates accessible through the site.

Moreover, even for studies properly considered “applicable clinical trials” for which registration and reporting of results on ClinicalTrials.gov is required, the site is not an adequate substitute for providing increased clarity and flexibility for manufacturers to convey information about those trials to HCPs and payors. For example, the law provides that clinical trial registration information for a pipeline device will not be posted on ClinicalTrials.gov until after it is approved or cleared by FDA for any use.⁹⁹ The law also expressly permits delays in submission of results to ClinicalTrials.gov in certain cases where the product or use studied in the clinical trial has yet not received FDA approval or clearance.¹⁰⁰ As a result, HCPs and payors who visit ClinicalTrials.gov on their own initiative will not commonly find the up-to-date, informative detail on pipeline products or new uses of marketed products that FDA restricts manufacturers from sharing in the current regulatory framework.

B. The Notice and Memorandum Do Not Address Other Important Alternatives

1. FDA Should Implement An Advisory Opinion Process As An Interim Step While It Conducts the Comprehensive Review Of Its Regulatory Approach

As MIWG has long advocated,¹⁰¹ FDA should adopt an advisory opinion process to allow manufacturers to obtain timely, binding advice from the agency with respect to proposed communication activities. Although an advisory opinion process would not fully address the issues raised by FDA’s current approach, it would be useful in mitigating the chilling effects of the existing scheme, particularly as an interim step while the agency continues its comprehensive review.

⁹⁸ See *id.* at 65105 (“In the future, we may consider developing tools to assist sponsors who provide optional results information for observational studies (other than certain pediatric postmarket surveillances of a device product that are not a clinical trial), which are outside the scope of this rule. The Agency does provide online access to results templates for interventional studies to assist and guide responsible parties in submitting results information under section 402(j) of the PHS Act[.]”). Additionally, the layout of the website itself is designed to assist potentially eligible research subjects in locating studies of interest – the inclusion of retrospective study data makes little sense juxtaposed against statements such as: “Talk with your doctor and family members or friends about deciding to join a study.” This statement is included under the “Contacts and Locations” section of the landing page for every clinical trial posted on the website.

⁹⁹ 42 U.S.C. § 282(j)(2)(D)(ii); see also 42 C.F.R. § 11.35.

¹⁰⁰ 42 U.S.C. § 282(j)(3)(E)(iii)-(v); see also 42 C.F.R. § 11.44(b)-(c).

¹⁰¹ See generally Amended Comments to Docket No. FDA-2009-N-0247 (Apr. 15, 2010).

a. In 2010, The MIWG Requested An Advisory Opinion Process, Which Was Rejected By The Transparency Task Force

In March 2010, FDA requested comments on ways to increase transparency between the agency and regulated industry, including comments on improvements that FDA could make in “[p]roviding useful and timely answers to industry questions about specific regulatory issues.”¹⁰²

In April 2010, the MIWG submitted written comments asking that FDA implement an advisory opinion process to provide timely and binding advice in response to specific requests on proposed industry activities involving promotional speech and scientific exchange regarding medical products.¹⁰³ As we explained, although off-label use is recognized by FDA as a constituent part of medical practice and sometimes even the standard of care, FDA guidance and policy is often unclear and hard to apply to specific proposed activities, particularly given the evolution in technology and business practices. Moreover, assessing a proposed activity is challenging because of the lack of clarity in the regulatory scheme and the associated need to maintain large regulatory staffs, escalation mechanisms to address differences of opinion, and other regulatory and compliance infrastructure. Often, despite significant investments in this infrastructure, manufacturers will decide against a proposed activity because of the lack of a prompt mechanism to obtain clear FDA feedback, even if the activity is lawful and would advance the public health.¹⁰⁴

Such self-censorship, and its attendant constitutional and public health disadvantages, could be ameliorated by a robust advisory opinion mechanism, as we asked FDA to establish in our 2010 submission. In that submission, we described the ways in which our proposed program would be consistent with analogous programs implemented by other agencies, including sibling agencies within the Department of Health and Human Services (HHS). Our submission also pointed out safeguards that would provide FDA and other stakeholders with assurance that the advisory opinion process could not be misused to circumvent regulatory safeguards.

FDA rejected the MIWG proposal in January 2011. According to FDA’s Transparency Task Force, an existing regulation already allows “companies to receive advisory comments on specific promotional pieces for drug and biological products before disseminating those pieces.”¹⁰⁵ But, for several reasons, the existing comment process is no substitute for the advisory opinion process requested by the MIWG.

¹⁰² Food and Drug Administration Transparency Task Force; Request for Comments, 75 Fed. Reg. 11893, 11894 (Mar. 12, 2010).

¹⁰³ See generally Amended Comments to Docket No. FDA-2009-N-0247 (Apr. 15, 2010).

¹⁰⁴ These challenges are particularly acute for startups, where the successful rollout of proposed activities for a startup’s first commercial product could have a significant impact on the company’s financial viability. See *supra* note 75.

¹⁰⁵ U.S. Dep’t of Health and Human Services, Transparency Task Force, *FDA Transparency Initiative: Improving Transparency to Regulated Industry* 44 (Jan. 2011) [hereinafter “Transparency Report”].

The relevant regulation (21 C.F.R. § 202.1(j)(4)) provides that:

Any advertisement may be submitted to [FDA] prior to publication for comment. If the advertiser is notified that the submitted advertisement is not in violation and, at some subsequent time, [FDA] changes its opinion, the advertiser will be so notified and will be given a reasonable time for correction before any regulatory action is taken under this section. Notification to the advertiser that a proposed advertisement is or is not considered to be in violation shall be in written form.

As an initial matter, the opportunity to seek comments under this regulation is limited to “submitting proposed . . . advertisements to FDA for advisory review before publicly disseminating them.”¹⁰⁶ It does not allow a company to seek comments on other issues, such as the legality of contemplated business practices. For instance, manufacturers cannot use § 202.1(j)(4) to obtain FDA’s advice on oral communications with HCPs or others, promotional activity at medical meetings, or the distribution of clinical practice guidelines. Those business practices are simply outside the scope of the regulation.

Further, even within the limited scope of advertisements, the regulation has not been implemented in a commercially reasonable manner. For many years, the practice of the Office of Prescription Drug Promotion (OPDP) has been to provide an initial round of comments but to withhold notification that a submitted piece is “not in violation” until the piece has been resubmitted, often several times. Each submission involves significant delay—OPDP must conduct its review, and may require input from the relevant review division, and neither OPDP nor the review division(s) are subject to any mandatory deadline. Years ago, FDA admitted that its “ability to keep pace with the demands for reviews has decreased, and the time it takes to review . . . materials submitted for advisory review . . . has been increasing.”¹⁰⁷ FDA also admitted that the “lack of timely, predictable FDA review times . . . has hindered companies’ ability to accurately set timeframes for their marketing campaigns and has discouraged companies from taking advantage of” the process set out in the regulation.¹⁰⁸ Since 2002, the agency “has been cited in two Government Accountability Office (GAO) reports” regarding its slow review times.¹⁰⁹ Unsurprisingly, some manufacturers find the delay involved in OPDP review so incompatible with operational needs that they decline to invoke the process at all.

Even when manufacturers do request review under § 202.1(j)(4), they are not likely to obtain usable advice in the first round of review. It is typical for an OPDP response to decree

¹⁰⁶ User Fee Program for Advisory Review of Direct-to-Consumer Television Advertisements for Prescription Drug and Biological Products; Request for Notification of Participation and Number of Advertisements for Review, 72 Fed. Reg. 60677, 60678 (Oct. 25, 2007). Although the regulation applies only to “advertisements,” FDA has interpreted 21 C.F.R. § 202.1(j)(4) to apply to both advertisements and promotional labeling materials.

¹⁰⁷ *Id.*

¹⁰⁸ *Id.*

¹⁰⁹ *DDMAC Promotion Review Times Are Too Slow, Drugmakers Say*, DRUG INDUSTRY DAILY (May 24, 2010).

that a specific statement in a promotional piece is “misleading” and to recommend “revising or deleting” the allegedly misleading language. But little or no advice is provided regarding the specific ways in which the statement can or should be revised. Furthermore, what little advice may be provided by one reviewer may not be consistent with the positions taken by other reviewers commenting on analogous promotional pieces, and may also conflict with applicable legal requirements. For example, FDA regulations permit the presentation of retrospective subgroup analysis provided that such analysis is not used “to discover and cite findings not soundly supported by the study, or to suggest scientific validity and rigor for data from studies the design or protocol of which are not amenable to formal statistical evaluations,”¹¹⁰ but OPDP reviewers have objected when manufacturers have sought to present retrospective subgroup analyses in a manner consistent with the regulation. The only option to obtain greater clarity is to submit an additional request for comments, with further attendant delays and no guarantee that additional comments will be any more helpful. Ultimately, most manufacturers are unable to pursue the advisory comment process through the multiple rounds of resubmission necessary to obtain a final “no comment” letter from OPDP, which is how OPDP signals that the submitted piece is “not in violation” within the meaning of § 202.1(j)(4).

Finally, 21 C.F.R. § 202.1(j)(4) is subject to additional limitations in scope that make it a poor substitute for the advisory opinion process requested by the MIWG. For instance, the regulation applies only to prescription drugs, and there is no corresponding process for medical devices. Even as to prescription drugs, OPDP has imposed limitations not found in the text of the regulation. OPDP does not review materials submitted under the advisory comment process if “the submitted materials, or substantially similar claims or presentations, have been disseminated or published—including after submission for comments.”¹¹¹ In addition, review of launch materials is limited to an advertisement and a promotional labeling piece for each of its two principal audiences (HCPs and patients) and one website. OPDP also imposes page limitations on the pieces that it will review (*e.g.*, the advertisement directed to HCPs must not exceed four pages, not including the brief summary).¹¹²

b. An Advisory Opinion Process Will Advance, Not Harm, The Public Health

The Task Force asserted that FDA’s current practices are “within the agency’s expertise” and “contribute[] to FDA’s mission.”¹¹³ These statements are not responsive to MIWG’s proposal. A functional advisory opinion process also would be within FDA’s expertise, and would improve FDA’s ability to “[p]roved[e] useful and timely answers to industry questions

¹¹⁰ 21 C.F.R. § 202.1(e)(7)(iii).

¹¹¹ FDA, Draft Guidance: Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs Guidance for Industry 8 (April 2015).

¹¹² *Id.* at 8-9.

¹¹³ Transparency Report at 44.

about specific regulatory issues,” which was the stated goal of the transparency initiative.¹¹⁴ It also would advance FDA’s public health mission by facilitating manufacturer communication of accurate information about regulated products—an objective that is not met by the existing advisory comment program.

Nor is there any merit to the Task Force’s assertion that a functional advisory opinion program “may place inappropriate restrictions on FDA’s ability to respond to emerging issues to best protect and promote the public health.”¹¹⁵ Although the report did not elaborate on this point, it appears to reflect concern that advisory opinions could preclude FDA from taking enforcement action in a particular instance in which action is warranted. That concern is simply meritless.

As we explained in 2010, several features of the proposed program would assure that advisory opinions issued by the Agency would be narrowly drawn and that any manufacturer activity that presents public health issues would be immediately subject to enforcement action. For example, requesters would outline a specific proposed course of action and would not seek feedback on questions of general legal interpretation, actions undertaken by parties other than the requestor, or conduct by the requestor that has already occurred or is occurring on an ongoing basis. Once FDA issues an opinion, it would post both the request and the opinion on its website in an easily searchable format similar to that available for FDA guidance documents.¹¹⁶ Advisory opinions would be legally binding only with respect to the requester. For other parties, advisory opinions may serve as nonbinding recommendations. Moreover, FDA’s current regulations on advisory opinions provide that FDA “may take appropriate civil enforcement action contrary to an advisory opinion before amending or revoking the opinion,” where a situation involves “an immediate and significant danger to health.”¹¹⁷ Thereafter, the regulation provides for expedited amendment or revocation of the advisory opinion involved.¹¹⁸ The safeguards that exist in that long-standing rule would apply with full force in this context and should be more than sufficient to address the concern identified in the Task Force report.

¹¹⁴ Food and Drug Administration Transparency Task Force; Request for Comments, 75 Fed. Reg. 11893, 11894 (Mar. 12, 2010).

¹¹⁵ Transparency Report at 44.

¹¹⁶ We suggest that FDA allow 30 days for public comment on each request for an advisory opinion and provide an advisory opinion within 90 days of accepting the request for filing. We believe FDA should consider implementing a system to charge a reasonable fee for the review of advisory opinion requests and the development and issuance of advisory opinions in response to those requests. We recognize that Congress likely would need to authorize the imposition of such a fee. Such an authorization could be discussed as part of the reauthorization of the Prescription Drug User Fee Act.

¹¹⁷ 21 C.F.R. § 10.85(f).

¹¹⁸ *Id.*

c. Administrative Law Principles Do Not Preclude Binding Advisory Opinions

As just discussed, FDA regulations currently provide for advisory opinions regarding questions of “general applicability.”¹¹⁹ Unfortunately, the advisory opinion process has been effectively abandoned by FDA.¹²⁰

In 1992, FDA proposed to substantially revise the advisory opinion regulation to state that no such opinion would be binding.¹²¹ The proposal claimed that a binding advisory opinion process is “inconsistent with the general principle that Federal Agencies may not be estopped from enforcing the law” and that “advisory opinions are not binding in court.”¹²² The proposal also claimed that issuing an advisory opinion without notice and comment is inconsistent with the requirements of the Administrative Procedure Act (APA), as interpreted by the court in *Community Nutrition Institute v. Young*, 818 F.2d 943 (D.C. Cir. 1987).¹²³ None of these assertions is correct.

As to estoppel, it is true that the government “may not be estopped on the same terms as any other litigant.”¹²⁴ The Supreme Court has not, however, endorsed the view that government agencies can *never* be estopped based on their representations to regulated industry.¹²⁵ Thus, courts can apply estoppel in enforcement actions brought by federal agencies.¹²⁶ Relevant here, courts have indicated that estoppel may apply if the agency attempts to act inconsistently with an “opinion” or “administrative interpretation” that remains in force.¹²⁷ That is because advisory

¹¹⁹ *Id.* § 10.85(a).

¹²⁰ *See, e.g.*, Letter from Susan H. Hargrove, Smith, Anderson, Blount, Dorsett, Mitchell & Jernigan, L.L.P. to Jane A. Axelrad, Assoc. Dir. For Policy, CDER (Sept. 9, 2009) (confirming telephone call during which FDA indicated that FDA “no longer issued advisory opinions”).

¹²¹ Administrative Practices and Procedures; Advisory Opinions and Guidelines, 57 Fed. Reg. 47314 (Oct. 15, 1992).

¹²² *Id.* at 47315.

¹²³ The proposed changes to § 10.85 were never finalized, although the proposal and its thesis that advisory opinions cannot be legally binding were mentioned in several later Federal Register notices. *See, e.g.*, Guidance Documents; The Food and Drug Administration’s Development and Use; Request for Comments, 61 Fed. Reg. 9181, 9183 n.1 (Mar. 7, 1996); The Food and Drug Administration’s Development, Issuance, and Use of Guidance Documents, 62 Fed. Reg. 8963 (Feb. 27, 1997); Administrative Practices and Procedures; Good Guidance Practices, 65 Fed. Reg. 56468, 56474 (Sept. 19, 2000).

¹²⁴ *Heckler v. Cmty. Health Servs., Inc.*, 467 U.S. 51, 60 (1984).

¹²⁵ *See Office of Personnel Mgmt. v. Richmond*, 496 U.S. 414, 423 (1990) (“[We] need not embrace a rule that no estoppel will lie against the Government”).

¹²⁶ *See, e.g., ATC Petroleum, Inc. v. Sanders*, 860 F.2d 1104, 1111 (D.C. Cir. 1988) (“[T]he fundamental principle of equitable estoppel applies to government agencies”).

¹²⁷ *Graham v. SEC*, 222 F.3d 994, 1007 (D.C. Cir. 2000). The older cases cited by FDA in the proposed rule are not to the contrary. For instance, in both *Bentex Pharm., Inc. v. Richardson*, 463 F.2d 363, 368-69 (4th Cir. 1972), and

opinions bind both the government and the requester, a principal that has been recognized by other HHS components¹²⁸ and the federal courts.¹²⁹

Finally, the advisory opinion process outlined above is clearly permissible under the APA. The court in *Community Nutrition Institute* found that a rule with present, binding effect across an entire industry is substantive and, therefore, requires notice and comment.¹³⁰ As proposed above, however, an advisory opinion would only bind the government as to those entities that join in the request (as is the case under CMS and OIG regulations), not the public at large. Moreover, the process outlined above actually involves notice through the Federal Register and an opportunity for public comment.

d. FDA Has Provided Advisory Opinions On A Selective Basis

Despite FDA's expressed reluctance to adopt a meaningful advisory opinion process, the agency has done so in limited circumstances when necessary to resolve litigation or enforcement actions. As these examples make clear, it is feasible for FDA to provide binding advice on proposed promotional activities and related communications.

First, in 1991, ICN Pharmaceuticals "agreed to inform FDA two days prior to any intended 'dissemination within the U.S. of findings or actions of foreign regulatory bodies relating to any new drug,' or any other disclosure necessary for 'the full exchange of scientific information.'" FDA agreed to review that manufacturer's scientific exchange communications

United States v. Articles of Drug . . . Hormonin, 498 F. Supp. 424, 435-37 (D.N.J. 1980), the courts refused to give effect to so-called "old drug" opinions that had been formally revoked through a Federal Register notice prior to the commencement of litigation. See *New-Drug Status Opinions; Statement of Policy*, 33 Fed. Reg. 7758 (May 28, 1968). Similarly, in *AMP Inc. v. Gardner*, 275 F. Supp. 410, 412-13 (S.D.N.Y. 1967), the court refused to give effect to an informal letter that had apparently been sent by the agency in error, had been subsequently "recalled," and was inconsistent with other correspondence.

¹²⁸ See, e.g., *Medicare and State Health Care Programs: Fraud and Abuse; Issuance of Advisory Opinions by the OIG*, 62 Fed. Reg. 7350, 7355 (Feb. 19, 1997) ("An advisory opinion issued under this process is legally binding on the Department (including the OIG) and the requester."); *Medicare Program; Physicians' Referrals; Issuance of Advisory Opinions*, 63 Fed. Reg. 1646, 1653 (Jan. 9, 1998) ("When we issue an advisory opinion under this process, it is legally binding on [CMS] and the requestor, but only with respect to the specific conduct of the particular requester.").

¹²⁹ See, e.g., *Unity08 v. FEC*, 596 F.3d 861, 864 (D.C. Cir. 2010) ("Advisory opinions have binding legal effect on the Commission.") (quoting *FEC v. Nat'l Rifle Ass'n of Am.*, 254 F.3d 173, 185, (D.C. Cir. 2001)). Once again, the older cases previously cited by FDA are not on point. In one case, the district court indicated (in dicta, in a footnote) that 21 C.F.R. § 10.85(j) could be read to suggest that a preamble statement did not impose a "legal standard by which [FDA's] actions" in granting certain extensions "should be judged," but then held that the standard had been "met on the facts of this case." *McIlwain v. Hayes*, 530 F. Supp. 973, 977 n.8 (D.D.C. 1981). In the other, the district court correctly noted that the plain text of § 10.85(j) provides only that "advisory opinions cannot impose additional enforceable legal obligations" on regulated industry. *United States v. Articles of Drug . . . Promise Toothpaste*, 594 F. Supp. 211, 218 (N.D. Ill. 1987). Ultimately, both cases show that the agency has the authority to define the effect of an advisory opinion through its regulations.

¹³⁰ 818 F.2d 943, 948-49 (D.C. Cir. 1987).

as a condition of resolving Department of Justice allegations regarding the promotion of Virazole (ribavirin) as a treatment for AIDS and related diseases.¹³¹

Second, in resolution of recent First Amendment litigation, the agency agreed that Amarin Pharma Inc. (Amarin) may submit up to two requests per calendar year “to determine if FDA has concerns with Amarin’s proposed communications.” FDA committed to responding “with its specific concerns or objections within 60 calendar days,” agreed that Amarin would have an opportunity to respond, and agreed that the agency would reply with “the specifics of any dispute that remains.”¹³²

These examples underscore the feasibility of an advisory opinion process for all stakeholders, which would also provide significant benefits. The opportunity to obtain detailed agency input on specific “real world” activities would provide the specific requester with a clear and binding roadmap for compliance. Furthermore, the public would be able to obtain additional insight through the agency’s application of the law in specific factual scenarios, and the agency could develop recommendations regarding communication practices in specific circumstances not explicitly addressed in its regulations and guidance documents.

e. An Advisory Opinion Process Would Help FDA Meet Its Obligations Under The First And Fifth Amendments

A functional advisory opinion process of the sort outlined above would not just benefit manufacturers, the public, and the agency. It also would be helpful in ensuring that FDA’s regulation of manufacturer speech is consistent with the First and Fifth Amendments. As noted above, the government is required to act with precision and clarity when attempting to regulate speech and, in general, must provide advance notice when purporting to prohibit promotional practices. At present, however, manufacturers contemplating changes to their business practices must search each new enforcement letter, speech, policy statement, guidance document, Federal Register notice, complaint, indictment, litigation paper, settlement, plea agreement, and press release to divine, as best as possible, whether FDA (or another relevant regulator) may later object. Providing binding advice would allow FDA to reduce some of these constitutional concerns through a procedural mechanism, even before FDA has completed its comprehensive review of the regulatory scheme or made any modifications to the regulations or FDA policies. And, given its inherent benefits, this advisory opinion process would remain valuable even in a regulatory environment that better harmonized FDA oversight with constitutional requirements.

2. FDA Should Address Other Proposals Offered By The MIWG

Over the years, the MIWG has offered a variety of additional proposals for FDA to consider as it modernizes its regulatory framework in light of relevant constitutional and

¹³¹ *ICN Settles Justice Dept. Virazole Aids Promotion Suit with \$600,000 Payment; Settlement Could Presage FDA’s Use of Civil Penalties in Ad Cases*, THE PINK SHEET (June 3, 1991).

¹³² Stipulation and Order of Settlement, *Amarin Pharma Inc. v. FDA*, ¶ 5, No. 15-3588 (S.D.N.Y. Mar. 8, 2016).

statutory limitations. We will not describe them in detail here,¹³³ but provide for the agency’s reference a high-level summary of some of these additional steps the agency could take to improve its regulatory process and lessen the constitutional concerns raised by its regulation of manufacturer speech.¹³⁴

First, as discussed *supra*, FDA should issue clear and binding regulations that provide manufacturers with certainty about the permissibility of their communications. Regulating truthful, non-misleading scientific and medical information through non-binding draft guidance documents and *ad hoc* warning and untitled letters raises Fifth Amendment concerns, as discussed *supra*, and impedes the public health by deterring manufacturers from generating and sharing valuable information with HCPs and payors. In clarifying its regulations, FDA should for example make clear that drug and medical device “labeling” comprises only those “written, printed, or graphic” materials that are within the statutory definition, as implemented by FDA in 21 C.F.R. § 1.3(a). As discussed in the MIWG’s recent petition, FDA should also revise the “intended use” regulations by removing the knowledge prong, removing the “circumstances surrounding distribution” prong, and any other language suggesting that FDA can find intended use irrespective of how the product is positioned in the marketplace.¹³⁵

Additionally, FDA should codify the definition of “scientific exchange” for drugs from the 1987 preamble language, and make parallel clarifying revisions to 21 C.F.R. § 812.7(a), and should also further clarify pathways under existing law for manufacturers to engage in “pipeline” communications with payors, institutional customers, and HCPs. Finally, FDA should revise its guidelines to assure sufficient latitude to distribute clinical practice guidelines. Truthful, non-misleading scientific and medical information is of value to HCPs and payors and furthers the public health, and FDA should ensure pathways for its robust dissemination.

III. CONCLUSION

The notice posed a broad range of questions about policy alternatives that do not refer to or even implicitly reflect any legal limitation on FDA’s ability to select from among options identified by the agency or other stakeholders, and the Memorandum largely reiterated FDA’s preferred policy positions without engaging in a proper constitutional analysis. As FDA continues with its comprehensive review, we believe the agency should put constitutional limitations at the forefront, and then identify the modifications that should be made to align the scheme more fully with the First and Fifth Amendments. Our prior submissions have described those changes in detail, and have also thoroughly described the statutory limitations on FDA’s authority to regulate manufacturer speech. These limitations also support the MIWG’s suggested approach, which would assure adequate avenues for manufacturer speech by clarifying the scope

¹³³ As referenced *supra* in note 7, MIWG has made 18 submissions to various FDA dockets that describe these and other proposals in greater detail.

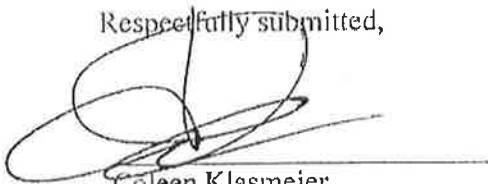
¹³⁴ We do not intend to suggest that these alternatives, whether alone or in combination, would remedy all the infirmities in FDA’s current approach.

¹³⁵ See Petition to Stay and for Reconsideration, Docket No. FDA-2016-N-1149-0048 (Feb. 8, 2017).

of existing safe harbors and better aligning the regulatory scheme with the FDCA and constitutional protections.

FDA should take this opportunity to “open the channels of communication, rather than . . . clos[ing] them” and embrace a regulatory framework that enables and supports a robust exchange of valuable information between manufacturers and learned audiences, such as healthcare providers and payors.¹³⁶ MIWG stands ready to support FDA as it moves toward a revised regulatory framework that recognizes and accepts the clear and long-standing First and Fifth Amendment restraints on its regulatory authority while also continuing to promote the agency’s ability to exercise regulatory oversight and protect the public health.

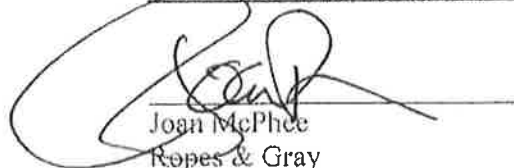
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¹³⁶ *Va. State Bd. of Pharm.*, 425 U.S. at 770.

Testimony of Kellie Combs On Behalf Of The Medical Information Working Group

Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products; Public Hearing; Request for Comments, 81 Fed. Reg. 60,299 (Sept. 1, 2016)

Good morning. I am Kellie Combs, a Partner in the Washington office of Ropes & Gray, and I am appearing here today, along with my colleague Coleen Klasmeier of Sidley Austin, on behalf of the Medical Information Working Group, an informal working group of manufacturers of biopharmaceutical products and medical devices. We thank FDA for granting our request to speak today.

The MIWG has long advocated for review – and, more importantly, reform – of the manner in which FDA regulates manufacturer speech. FDA’s framework for regulating manufacturer communications sharply limits the extent to which manufacturers may share truthful and non-misleading information that is not contained in the FDA-approved or –cleared product labeling.ⁱ This framework is at odds with public policy goals, and raises fundamental First and Fifth Amendment issues.

Members of the MIWG have made 17 submissions to FDA dockets over the last ten years on these topics,ⁱⁱ including two citizen petitions in 2011 and 2013.

Both of our petitions were granted in June 2014. At that time, FDA said that it was engaged in a “comprehensive review of its regulations and guidance documents in an effort to harmonize the goal of protecting the public health with First Amendment interests.”ⁱⁱⁱ FDA also said that the agency planned to take a series of concrete actions by issuing guidance on four topics by the end of 2014. FDA still has not issued those four guidance documents. We are concerned by the amount of time that has elapsed without FDA having taken even the

incremental steps the agency has promised to take in order to provide clarity to industry, much less the larger step of comprehensively reviewing its regulations and policies as necessary in view of constitutional limitations. We are also concerned that the framework that FDA has adopted in announcing this public hearing will not contribute to accomplishing either the incremental steps or the larger goal.

The agency has long recognized that off-label prescribing is central to public health interests. As an illustrative recent example, a senior FDA official submitted a Declaration in the *Amarin* litigation acknowledging that prohibiting off-label use would, in her words, “substantially restrict the discretion and independence of healthcare providers, and would fail to take into account the interests behind allowing healthcare providers to determine the best treatment options for individual patients in specific circumstances[.]”^{iv}

Recognizing the essential importance of off-label *prescribing* to the public health, FDA has repeatedly underscored the critical need for accurate *information* about off-label uses.

Put another way, FDA acknowledges that, in the absence of FDA-approved prescribing information to support an off-label use, there is a need for truthful, non-misleading, clinically relevant information to assist prescribers in making well-informed treatment decisions for their patients. As far back as 1972, FDA acknowledged that, once a product is on the market, physicians are then “responsible for making the final judgment as to which, if any, of the available drugs patients will receive in light of the information contained in their labeling and other adequate scientific data available” to the treating physician.^v The dissemination of up-to-date medical information about a product—irrespective of the information in the product’s

labeling—helps to guide treatment decisions and ensures that patients receive care based on current, sound, scientific and clinical information.^{vi}

We share FDA’s view that good public policy favors providing prescribers with truthful and non-misleading information about off-label uses. Indeed, “because the pace of medical discovery runs ahead of FDA’s regulatory machinery,”^{vii} off-label uses may in many instances be “state-of-the-art” or as well-established by scientific data as labeled uses. And for many diseases and conditions, off-label uses either are the only therapies available, or are the therapies of choice, particularly in certain fields of medicine such as oncology or psychiatry. Manufacturers often are in possession of the best and most current information available about their products, and may be the *only* source of such information. To facilitate informed health care decision-making and enhance patient care, FDA must ensure that there are clearly defined and effective pathways for manufacturers to responsibly communicate about their products, even if that information does not appear in official labeling.

FDA’s current regulatory approach, however, generally prohibits manufacturers from speaking about unlabeled uses unless an ill-defined, often non-binding “safe harbor” applies. That approach not only impedes access to truthful, non-misleading product information, but also conflicts with constitutional dictates. FDA acknowledged, in its 2014 letter granting MIWG’s citizen petitions, “the evolving legal landscape in the area of the First Amendment.”^{viii} Implicit in FDA’s statement is the recognition that the Constitution sets boundaries on permissible governmental regulation and punishment of truthful and non-misleading manufacturer speech.

And yet, in announcing this hearing, FDA does not fulfill its promise on unsolicited requests, scientific exchange, payor communications, or clinical practice guidelines. Clarity on those topics was essential in 2011, when MIWG submitted its first citizen petition, remained so in 2014 when FDA granted our petitions, and continues to be critical today. Moreover, in failing to address or even mention First and Fifth Amendment dictates, the hearing notice itself suggests that the agency does not appreciate, or may be unwilling to accept, the limitations imposed by the Constitution.

MIWG has a decade-long history of engagement with FDA and has urged the agency to be mindful of constitutional considerations as it develops policies governing manufacturer speech. The law requires no less. As the Supreme Court indicated in *Sorrell*, and other courts have confirmed recently, the First Amendment protects truthful and non-misleading speech by manufacturers. Accordingly, it is not manufacturers who must prove to the government the value of their truthful and non-misleading communications. The Constitution *itself* recognizes that value. As far back as 1976, in the *Virginia Board* decision, the Supreme Court recognized that both the speaker and listener have First Amendment rights to communicate and to receive information, regardless of its perceived worth by the government. To quote from the Supreme Court's 1993 decision in *Edenfield v. Fane*: "The commercial marketplace, like other spheres of our social and cultural life, provides a forum where ideas and information flourish. . . . [And] the general rule is that the speaker and the audience, not the government, assess the value of the information presented."^x The importance of protecting the "free flow" of information, to quote from *Sorrell*, "has great relevance in the fields of medicine and public health, where information can save lives."^x Under our Constitution, then, it is not the speech that must be

justified, but rather governmental restrictions on that speech, and they must be narrowly drawn to advance compelling government interests. As *Sorrell* tells us, “[i]n the ordinary case, it is all but dispositive to conclude that a law is content-based.”^{xi} Because FDA’s speech-restricting regulations “impose[] speaker- and content-based burden[s] on protected expression”—meaning they apply only to one set of speakers and they restrict what those speakers may say—they are subject to “heightened scrutiny” and are, in the Court’s words, “presumptively invalid.”^{xii}

In addition to vital First Amendment interests, FDA’s regulatory scheme also implicates the Due Process Clause of the Fifth Amendment, which requires government agencies to establish clear rules that give fair notice of what is prohibited.^{xiii} As the Supreme Court held in the *Fox II* decision, “when speech is involved, rigorous adherence to [Fifth Amendment] requirements is necessary to ensure that ambiguity does not chill protected speech.”^{xiv} While the agency has articulated narrow “safe harbors” for manufacturers to convey off-label information, it has never issued binding rules to put regulated industry on notice of where the lines are between off-label communications the agency considers lawful and those it does not.

Currently, in key respects FDA’s policy on off-label communications is conveyed through draft guidance. Because this guidance is in draft, it does not address concerns conveyed by industry and other stakeholders through public comment. The adoption of clear, binding rules is essential to bring FDA’s regulatory scheme into alignment with the Fifth Amendment.

Any meaningful review of the regulatory framework must revise the agency’s regulations and policies in view of First and Fifth Amendment limitations. And yet, the notice for today’s hearing contains only a single, passing reference to undescribed “developments

in . . . constitutional law.”^{xv} Rather than asking how to conform agency regulations to constitutional requirements, the notice starts from the premise that FDA has the authority to determine for itself what truthful, non-misleading speech is valuable for practitioners, and to decide, as a matter of policy, what speech it will permit. That is not how the Constitution works. The agency will be ill-equipped from this public process both to address comments in response to the notice and to fulfill its obligation to develop binding rules that are consistent with the Constitution. Any viable path forward must place the constitutional analysis in the foreground.

And now I will turn to Coleen Klasmeier.

Testimony of Coleen Klasmeier On Behalf Of The Medical Information Working Group

Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products; Public Hearing; Request for Comments, 81 Fed. Reg. 60,299 (Sept. 1, 2016)

I am Coleen Klasmeier of Sidley Austin, LLP, in Washington, DC.

[Slide 9: Agency Action Requested by MIWG] Over ten years the MIWG has advanced a range of proposals to help FDA achieve consistency with constitutional dictates in the regulatory scheme and articulated the various rationales supporting those proposals. In our first petition in July 2011, we focused on the lack of clarity in the regulatory scheme and the importance of clear rules. We asked FDA to affirm and clarify its policies on responses to unsolicited requests and scientific exchange. We also asked FDA to address payor-directed communications and the distribution of third-party clinical practice guidelines. In our petition, we focused on *statutory* limitations on FDA's authority. Though we recognized the utility of guidance, we asked that FDA provide the necessary clarity in **regulations**.

More than two years passed before we filed a second petition in 2013. We reiterated our request for clarity in the four specific areas outlined in the 2011 petition. We also indicated, however, that intervening judicial decisions had brought First and Fifth Amendment issues into the foreground.

In the 2013 petition, we suggested changes in FDA policies to illustrate the kinds of modifications we thought necessary to improve the regulatory scheme given constitutional principles and developments in the case law. In October 2014, several months after FDA had granted our petitions, we submitted a white paper to FDA. It identified some key proposals that we believed FDA should evaluate as part of its comprehensive review.

As Kellie mentioned, FDA promised in 2014 to issue guidance on unsolicited requests, scientific exchange, payor communications, and clinical practice guidelines. I want to address all of our proposals, including those relating to the four topics I just mentioned, but in doing so, I want to be clear: FDA recognized over two years ago that it had the information it needed to provide the guidances it promised, and the agency should not cite this hearing to justify further delay in fulfilling that promise. Instead, those guidances should issue promptly, and those modest first steps should serve as the starting point for the more comprehensive review in which the agency has said it is engaged.

One of our most significant proposals concerns the development of **scientific exchange regulations**. Scientific exchange is a type of non-promotional communication that includes scientific findings disseminated by or on behalf of product developers about investigational products and new uses of marketed products. Robust scientific exchange is critical because prescribers must make treatment decisions for their patients based on a range of information, including information that is not contained in the product labeling. FDA has never clearly delineated when a communication qualifies as scientific exchange, or what FDA contends is subject to regulation as advertising or labeling. This lack of clarity chills manufacturers from sharing important medical and scientific information about their products and raises serious questions under the Constitution.

The MIWG has also proposed that FDA confirm **the legal definition of “labeling.”** FDA should issue new interpretive guidance confirming the scope of “labeling.” Currently, manufacturers do not have clear guidance as to the types of communications that are within the key statutory definition, and the lack of clarity undermines the ability of payors,

practitioners, and patients to receive high-quality information. The purpose of this proposal is to bring much-needed clarity to the definition of “labeling,” which defines the main category of manufacturer communication that FDA is empowered to regulate under the law.^{xvi}

Our third proposal is that FDA amend **the regulatory definitions of “intended use.”** FDA published a proposed rule last year in partial response. Under the proposal, FDA would no longer be able to point to a manufacturer’s mere knowledge that its product is being used off-label to support a misbranding action under the statutory “adequate directions” provision. In our comments, we identified the ways in which FDA’s proposal did not go far enough. FDA has not yet finalized the rule.

The MIWG has also asked FDA, on several occasions, to assure that agency policies are sufficiently well-defined to avoid chilling important scientific speech that is necessary for informed decision-making by prescribers and fully informed policy design and coverage determinations by payors. We have asked FDA to address the need for managed care organizations and related entities to have sufficient access to information about both investigational and marketed medical products.

Manufacturers are chilled from providing information relevant to coverage and reimbursement decisions because FDA has not yet addressed payor-directed communications in a meaningful way. FDA’s general policies on manufacturer communications are not sufficient to address the informational needs presented by the managed care environment. In 2014, we submitted a memorandum to FDA describing the very specific ways in which we believe FDAMA section 114 should be interpreted. Although we understood at the time that FDA was

committed to developing guidance on payor-directed communications, including FDAMA 114 guidance, no interpretive statements or compliance recommendations have been issued.

The lack of guidance on FDAMA 114 is especially problematic. For one thing, in the current health care delivery environment, it has never been more important for manufacturers to have the ability to provide complete and accurate product information to support coverage and reimbursement decisions. This information must be provided in both the pre- and post-approval settings. For another, the lack of guidance means that manufacturers are uncertain as to FDA's interpretation of the "directly relates" prong of section 114. As you know, a senior FDA official made a presentation in 2012 that has been widely interpreted to mean that a manufacturer can only communicate economic analysis under FDAMA 114 if the analysis is premised on clinical endpoints that provided the basis for FDA's approval of the product. If that is the correct interpretation of the statute, then FDAMA 114 is of not much use. Payors need information that is not derived solely from analyses of data concerning endpoints that have been selected to support regulatory decision making. For FDAMA 114 to have any real force, it must be interpreted to mean that a manufacturer is permitted to provide information derived from analyses of data concerning endpoints that are related to those in official labeling, but are not the endpoints used in the registration trials and do not appear in labeling.

A closely related point is the lack of clarity in FDA policy respecting the difference between information that is "out of label" and information that is "off-label." We believe it is very clear that a manufacturer is permitted to provide accurate, scientifically supported information if the information is consistent with the labeling – meaning it stops short of promoting an entirely new use. FDA has not issued any public document of which we are

aware that explains the agency's interpretation of the law on this point. Manufacturers therefore do not have the benefit of an authoritative FDA position on when information that is not directly lifted from approved or cleared labeling is potentially regarded by the agency as prohibited off-label promotion.

Although policy discussions in this area have tended to focus on "off-label" information, in fact the regulatory climate is equally uncertain, and speech is unduly chilled, with respect to information on labeled indications and patient populations, where the substantiation standard can be far too rigid and excludes valuable data to the detriment of patients and prescribers. It is also challenging for manufacturers to navigate in the area of pipeline communications – those relating to products undergoing the research and development process. Payors need access to information about investigational products early enough to support coverage and reimbursement decisions. Waiting until after approval, or for an unsolicited request from a payor, can limit patient access and is not sufficient to meet this need.

More than six years ago we also requested that FDA revive the **advisory opinion mechanism** so that manufacturers could obtain advice from FDA regarding their proposed activities. Advisory opinions are used by other agencies, including by other components of HHS under other health care statutes such as the Anti-Kickback Statute.^{xvii} Our request was summarily denied.^{xviii} We continue to believe that it would encourage compliance with the law and help avoid unduly chilling beneficial speech if FDA were to accept our suggestion. We ask FDA to give immediate and serious consideration to establishing a process to enable manufacturers to obtain advice from FDA on specific activities involving the dissemination of information that is not set forth in approved or cleared labeling.

Ultimately, FDA must assure that its regulatory scheme for manufacturer communications respects constitutional and statutory limitations. [Slide: Proposed Approach]

We have proposed a wide variety of targeted modifications based on changes to the health care delivery system, shifting societal expectations, and developments in the case law.

FDA said more than two years ago that it would issue guidelines in four key areas. This hearing cannot justify additional delay in doing so. FDA should publish the guidances immediately, and these modest first steps should serve as the starting point for the more comprehensive review that FDA says it has undertaken.

We appreciate the time that we were given to present our views.

Thank you

ⁱ Consistently with FDA parlance, this includes labeling that has been approved or cleared by FDA, as well as labeling that is authorized to accompany a medical device product that is exempt from premarket notification requirements. See, e.g., FDA, Guidance for Industry, Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices at 1 n.2 (Dec. 2011).

ⁱⁱ These include responses to FDA’s requests for comments on scientific exchange (76 Fed. Reg. 81,508 (Dec. 28, 2011)), the draft guidance on responses to unsolicited requests (76 Fed. Reg. 82,303 (Dec. 30, 2011)), and revised draft guidance on reprints and related materials (79 Fed. Reg. 11,793 (Mar. 3, 2014)). The MIWG and its members have made these submissions to the Agency since 2008: (1) Comments, Draft 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, Docket No. FDA-2008-D-0053 (Apr. 18, 2008); (2) Amended Comments, FDA Transparency Task Force, Docket No. FDA-2009-N-0247 (Apr. 15, 2010); (3) Citizen Petition, Docket No. FDA-2011-P-0512 (July 5, 2011); (4) Comments re: Scientific Exchange and Responses to Unsolicited Requests, Docket Nos. FDA-2011-N-0912 and FDA-2011-D-0868 (Mar. 27, 2012); (5) Comments re: FCC v. Fox Television Stations Inc., and United States v. Caronia, Docket Nos. FDA-2011-P-0512 and FDA-2011-D-0868 (Mar. 1, 2013); (6) Comments, CDER Medical Policy Council, Docket No. FDA-2013-N-0206 (July 16, 2013); (7) Citizen Petition, Docket No. FDA-2013-P-1079 (Sept. 3, 2013); (8) Comments, *Food and Drug Administration Safety and Innovation Act Section 907 Report*, Docket No. FDA-2013-N-0745 (Nov. 20, 2013); (9) Comments, Draft Guidance for Industry: Fulfilling Regulatory Requirements for Postmarketing Submissions of Interactive Promotional Media for Prescription Human and Animal Drugs and Biologics, Docket No. FDA-2013-N-1430 (Apr. 14, 2014); (10) Comments, Draft Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices, Docket No. FDA-2008-D-0053 (May 2, 2014); (11) Comments re: FDA’s Draft Strategic Priorities for 2014–2018, Docket No. FDA-2014-N-0833 (July 31, 2014); (12) Comments, Draft Guidance for Industry: Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products—Recommended Practices, Docket No. FDA-2014-D-0758 (Aug. 25, 2014); (13) Comments, Draft Guidance for Industry: Internet/Social Media Platforms with Character Space Limitations—Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices, Docket No. FDA-2014-D-0397 (Sept. 16, 2014); (14) Comments, Draft Guidance for Industry: Internet/Social Media Platforms: Correcting Independent Third-Party Misinformation About Prescription Drugs and Medical Devices, Docket No. FDA-2014-D-0447 (Sept. 16, 2014); (15) Memorandum Re: Use of Health Care Economic Information Under Section 114 of the Food and Drug Administration Modernization Act, Docket No. FDA-2013-P-1079-0007 (Oct. 31, 2014); (16) White Paper: *Systemic, Societal, and Legal Developments Require Changes to FDA’s Regulation of Manufacturer Speech*, Docket No. FDA-2013-P-1079-0007 (Oct. 31, 2014); (17) 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,” Docket No. FDA-2015-N-2002-1876 (Nov. 24, 2015).

ⁱⁱⁱ Letter from Leslie Kux, Assistant Commissioner for Policy, to Alan R. Bennett, Joan McPhee, Paul Kalb, & Coleen Klasmeier, Docket Nos. FDA-2011-P-0512 and FDA-2013-P-1079, 8 (June 6, 2014).

^{iv} Declaration of Janet Woodcock, *Amarin Pharma, Inc. v. FDA*, No. 1:15-cv-03588-PAE (Jul. 7, 2015) (Dkt. 52 at 43).

^v Legal Status of Approved Labeling for Prescription Drugs, 37 Fed. Reg. 16,503, 16,504 (Aug. 15, 1972) (emphasis added).

^{vi} For example, the Associate Commissioner for Health Affairs at FDA wrote in 1992 that “the very latest information that can be of value to physicians . . . must be made available as soon as possible. Frequently, unlabeled use information is extremely important.” Stuart Nightingale, *Unlabeled Uses of Approved Drugs*, 26 Drug Info. J. 141, 145 (1992).

^{vii} *Richardson v. Miller*, 44 S.W. 3d 1, 13 n.11 (Tenn. Ct. App. 2000).

^{viii} Letter from Leslie Kux, Assistant Commissioner for Policy, to Alan R. Bennett, Joan McPhee, Paul Kalb, & Coleen Klasmeier, Docket Nos. FDA-2011-P-0512 and FDA-2013-P-1079, 10 (June 6, 2014).

^{ix} *Edenfield v. Fane*, 507 U.S. 761, 767 (1993).

^x *Sorrell v. IMS Health Inc.*, 564 U.S. 552, 567 (2011).

^{xi} *Id.* at 571.

^{xii} *Id.*

^{xiii} *FCC v. Fox Television Stations, Inc.*, 132 S. Ct. 2307, 2318 (2012) (quoting *United States v. Williams*, 553 U.S. 285, 304 (2008)).

^{xiv} *Id.* at 2317.

^{xv} Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products, 81 Fed. Reg. at 60,300.

^{xvi} In our 2013 petition, we also asked FDA to clarify the definition of advertising and therefore the scope of the advertising provisions in Sections 502(n) and (r) of the FDCA. For the sake of brevity, our oral testimony does not recapitulate that request.

^{xvii} MIWG, Amended Comments dated Apr. 15, 2010 re: Food and Drug Administration Transparency Task Force Request for Comments, Docket ID No. FDA-2009-N-0247.

^{xviii} See Transparency Task Force, DHHS, FDA Transparency Initiative: Improving Transparency to Regulated Industry, § V.A (2011).