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."[ix] 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

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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).