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CITIZEN PETITION

This petition is submitted under 21 C.F.R. § 10.30 on behalf of members of the Medical Information Working Group (MIWG). The MIWG is an informal working group of major manufacturers of prescription drugs and medical devices (including biological products).¹ The MIWG was formed to consider issues relating to the federal government's regulation of truthful, non-misleading, scientifically substantiated manufacturer communications about new (or "off-label") uses of approved drugs and approved/cleared medical devices.²

In 2008, the MIWG submitted comments to FDA on the draft guidance providing good practices for manufacturer distribution of reprints of scientific and medical journal articles and reference texts. In 2010, the MIWG submitted comments to FDA's Transparency Task Force, requesting that FDA use the advisory opinion process already established by FDA regulations to provide manufacturers with an administrative mechanism to seek binding advice from FDA on proposed activities involving the dissemination of off-label information. On July 5, 2011, a subset of MIWG members submitted a Citizen Petition to FDA, asking the Agency to clarify its regulations and policies for four types of manufacturer communications about off-label uses: (1) responses to unsolicited requests; (2) scientific exchange; (3) communications to

¹ The petition is submitted on behalf of: Allergan, Inc.; Bayer Healthcare Pharmaceuticals Inc.; Boehringer Ingelheim Pharmaceuticals, Inc.; Eli Lilly and Company; Genentech, Inc.; GlaxoSmithKline LLC; Johnson & Johnson; Novartis Pharmaceutical Corporation; Novo Nordisk, Inc.; Pfizer, Inc.; Purdue Pharma L.P.; and Sanofi US.

² Although "off-label use" is sometimes used to refer to any variation to the conditions of use described in the FDA-approved or -cleared labeling for a drug or medical device, many such variations may lawfully be discussed by manufacturers in promotional communications, and a manufacturer's promotion is not limited to statements in the approved or cleared labeling. In this document, "off-label use" and "new use" are used interchangeably, 59 Fed. Reg. 59,820, 59,820 (Nov. 18, 1994) ("Uses that do not appear in the labeling and are not approved by the agency are referred to as 'unapproved,' 'unlabeled,' 'off-label,' or 'extra-label' uses."), and "approved" also includes FDA clearance of medical devices under Section 510(k) of the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 360(k). Moreover, where we ask FDA to provide clarity in the regulatory framework respecting off-label use, we intend for that clarity to apply to all potential departures from approved labeling that, in FDA's view, constitute off-label uses.

formulary committees, payors, and similar entities; and (4) dissemination of third-party clinical practice guidelines.³

The MIWG acknowledges that FDA has responded to the July 2011 citizen petition in part, by proposing new draft guidance on responses to unsolicited requests.⁴ The MIWG further recognizes that FDA published a Federal Register notice on December 28, 2011 (76 Fed. Reg. 81,508) establishing a docket to receive comments and information on “scientific exchange,” to assist with the Agency’s evaluation of its policies on communications and activities related to off-label uses. Nevertheless, the MIWG respectfully requests that the Commissioner of Food and Drugs immediately take further steps to reevaluate, and modify as necessary, the Agency’s regulations and policies with respect to manufacturer dissemination of new-use information in light of public health considerations, statutory limitations, and recent First and Fifth Amendment case law.

As noted, the July 2011 petition requested that FDA take action to clarify the Agency’s regulations and policies with respect to four specific forms of off-label communication. The July 2011 petition sought to advance the public health through targeted action to clarify certain “safe harbors” for manufacturer communications about off-label uses. Over the past two years, however, the federal courts have decided several cases that implicate the very foundations of FDA’s regulations and policies governing manufacturer dissemination of information about off-label uses. These cases—Sorrell v. IMS Health, Inc., 131 S. Ct. 2653 (2011), FCC v. Fox Television Stations, 132 S. Ct. 2307 (2012) (Fox II), and United States v. Caronia, 703 F.3d 149 (2d Cir. 2012)—reiterate the First and Fifth Amendment requirements for clarity in the rules governing manufacturer communications, and for the Agency to both adequately justify and appropriately tailor its regulatory regime. Although the MIWG remains committed to working with FDA on measures to bring much-needed clarity in the four specific areas outlined in the July 2011 petition, we believe that these recent judicial decisions require thoughtful consideration of more fundamental change.

We write today to set forth our views as to the principles that emerge from the relevant constitutional provisions explicated by these and other judicial decisions. We write, as well, to explain our perspective on the approach that FDA should take in assuring that the foundation of the regulatory scheme is consistent with these principles. The MIWG believes that FDA should conform its regulations and policies governing manufacturer speech about off-

³ The MIWG or its members have made six submissions to the agency addressing promotional issues. See MIWG, Comments re: FDA Guidance on Good Reprint Practices, Docket No. FDA-2008-D-0053 (Apr. 18, 2008); MIWG, Amended Comments re: Food and Drug Administration Transparency Task Force Request for Comments, Docket No. FDA-2009-N-0247 (Apr. 12, 2010); Citizen Petition, Docket No. FDA-2011-P-0512 (July 5, 2011); MIWG, Comments re: Scientific Exchange, Docket Nos. FDA-2011-N-0912 and FDA-2011-D-0868 (Mar. 27, 2012); MIWG, Comments to Docket Nos. FDA-2011-P-0512 and FDA-2011-D-0868 (Mar. 1, 2013); MIWG, Comments re: CDER Medical Policy Council Request for Comments, Docket No. FDA-2013-N-0206 (July 16, 2013). The MIWG has also participated as amicus curiae in litigation relating to the role of manufacturers in distributing information containing information about new uses. See Brief Amicus Curiae for MIWG, United States v. Caronia, 703 F.3d 149 (2d Cir. 2012) (No. 09-5006-CR).

⁴ 76 Fed. Reg. 82,303 (Dec. 30, 2011); FDA, Draft Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices (Draft Guidance on Unsolicited Requests) (Dec. 2011), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM285145.pdf>.

label uses with the Agency's primary enabling statute, the Federal Food, Drug, and Cosmetic Act (FDCA). Our review of the statutory text and legislative history indicates that FDA can both protect the public health and satisfy constitutional limitations by ensuring that relevant regulations and guidance documents in the area of manufacturer speech about off-label uses are consistent with the labeling and advertising provisions of the FDCA. Our recommended approach is described below.

As FDA considers this petition, the MIWG wishes to emphasize several points:

- The MIWG's members are committed to compliance. Nothing in this petition should be construed to reflect any intention on the part of the member companies to support a material shift in the rigorous compliance standards that the biopharmaceutical and medical device industries have generally adopted. Robust monitoring systems for field-based activities and careful control over the ways in which our products are promoted remain a vital part of our operations.
- The members of the MIWG are committed to the development of high-quality data and information to satisfy the needs of a full range of stakeholders, including patients, practitioners, payors, and regulatory authorities. We have no intention of advocating that FDA depart from the Agency's practice of generally requiring two adequate and well-controlled trials to provide "substantial evidence" in the new drug approval. Nor do we intend to suggest that FDA abandon its commitment to an appropriately demanding interpretation of the "valid scientific evidence" standard in the medical device context.
- We are not purporting to provide the Agency with a single, comprehensive solution to the problem that we have identified—that the current scheme is insufficiently well-defined, precise, and speech-enabling to satisfy constitutional and statutory limitations. The significant constitutional concerns arising out of FDA and DOJ's implementation of the regulatory scheme can be ameliorated, but not fully resolved, by the targeted modifications that we set forth below in II.E. We nevertheless believe it is important that FDA at least begin to address the deficiencies in the current approach, and that it is vitally important for FDA to do so through an appropriately inclusive process.
- We believe FDA's objective should be to assure that the regulatory scheme adequately respects statutory and constitutional limitations so that it can protect and promote the public health for decades to come. Changes in the health care delivery system and in the expectations of patients, practitioners, and payors for information about medical products and other health care interventions make it an appropriate time for FDA to consider changes to the current regulatory approach that will assure its continued viability and relevance in a rapidly changing health care environment.

I. ACTIONS REQUESTED

The MIWG requests that FDA:

(1) Respond fully and in a constitutionally permissible manner to the four specific requests set forth in the July 2011 Citizen Petition. In particular, as discussed in further detail in Part II.D, *infra*, we request that FDA: (a) complete the policy development process, albeit with some mid-course correction in recognition of the emerging case law, in the

two areas in which FDA has already taken some action—responses to unsolicited requests and scientific exchange; and (b) initiate notice-and-comment rulemaking in the two areas in which FDA has not already taken action—manufacturers' communications with payors and similar entities about off-label uses (and investigational products) and manufacturer dissemination of third-party clinical practice guidelines that include information about off-label uses.

(2) Comprehensively review, and modify as necessary in view of constitutional and statutory limitations, the regulatory regime governing manufacturer communications to protect and promote the public health. We have suggested in Part II.E, *infra*, changes to FDA policies relating to: (1) the definition of "labeling" in Section 201(m) of the FDCA, 21 U.S.C. § 321(m); (2) the scope of the drug and medical device advertising provisions in Section 502(n) and (r) of the statute, 21 U.S.C. §§ 352(n),(r); and (3) the "intended use" definition in FDA regulations promulgated under Section 502(f)(1) of the statute (21 U.S.C. § 352(f)(1)), 21 C.F.R. §§ 201.128 & 801.4. We emphasize that these suggestions are intended to be illustrative and are not intended to comprise an exhaustive list of proposed modifications. We believe that FDA should consider the full range of possible changes to the regulatory scheme based on input from a wide range of stakeholders, including patients, prescribers, and payors as well as manufacturers and product developers.

II. STATEMENT OF GROUNDS

Our Statement of Grounds is organized as follows. Part II.A sets forth the public health rationale for the actions requested above. Part II.B sets forth three key principles that emerge from the Free Speech Clause of the First Amendment and the Due Process Clause of the Fifth Amendment and apply to FDA's regulation of manufacturer speech about off-label uses. Part II.C explains the applicability of these principles to the four specific requests from the July 2011 petition. Part II.D provides the MIWG's rationale supporting our request for a comprehensive analysis of, and necessary modifications to, the FDA regulatory regime governing manufacturer communications about off-label uses of approved drugs and medical devices. Part II.E sets forth a non-exhaustive list of suggested modifications to the regulatory scheme that would better align FDA's approach with relevant constitutional limitations and protect and promote the public health.

A. REVIEW OF AND CHANGES TO THE CURRENT REGULATORY SCHEME ARE NECESSARY TO PROTECT AND PROMOTE THE PUBLIC HEALTH

The primary rationale supporting changes to the current regime unequivocally proceeds from public health considerations. For many years, FDA has recognized that prescribing decisions are not exclusively informed by approved labeling.⁵ “Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgment.”⁶ Indeed, as FDA has acknowledged, “off-label uses or treatment regimens may be important and may even constitute a medically recognized standard of care.”⁷ A bedrock principle of FDA regulation of drugs and medical devices, therefore, is that some manufacturer dissemination of information about off-label uses is appropriate for the promotion of patient care.

Over many years, FDA has developed policies and promulgated regulations to facilitate such information dissemination. Manufacturers are permitted to provide off-label use information in accordance with four “safe harbors”: (1) as part of “scientific exchange,” 21 C.F.R. § 312.7(a); (2) in response to unsolicited requests, 59 Fed. Reg. 59,820, 59,823 (Nov. 18, 1994); (3) in the context of continuing medical education (CME) and other “scientific and educational activities,” 62 Fed. Reg. 64,074 (Dec. 3, 1997); and (4) in medical journal articles and scientific or medical reference publications disseminated to prescribers and healthcare entities, 74 Fed. Reg. 1,694 (Jan. 13, 2009). At the same time, FDA has emphasized the importance of enforcing the FDCA against manufacturer “promotion” of off-label uses. 59 Fed. Reg. 59,821-25. The resulting policy is one of “balance,” between allowing communication of reliable scientific information regarding off-label uses and limiting off-label promotion. *Id.* at 59,825; see also 61 Fed. Reg. 52,800, 52,800 (Oct. 8, 1996) (noting that agency policies should “strike the proper balance between the need for an exchange of reliable scientific data and information within the health care community, and the statutory requirements that prohibit companies from promoting products for unapproved uses”); 57 Fed. Reg. 56,412, 56,412 (1992) (same).

Against this backdrop, Congress has enacted legislation to revolutionize the health care delivery system. The Patient Protection and Affordable Care Act of 2010 (PPACA), among many other changes, established the Patient-Centered Outcomes Research Institute (PCORI), a new public-private entity empowered to encourage those involved in clinical and health services research to include the patient’s perspective and patient-oriented outcomes in their work.⁸ Patient-centered care was also a focus of the President’s Council of Advisors on

⁵ 37 Fed. Reg. 16,503, 16,503 (Aug. 15, 1972).

⁶ FDA, “Off-Label” and Investigational Use of Marketed Drugs, Biologics, and Medical Devices – Information Sheet (last updated Aug. 10, 2011) (available at www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm); see also 63 Fed. Reg. 31,143, 31,153 (June 8, 1998) (“FDA has long recognized that in certain circumstances, new (off-label) uses of approved products are appropriate, rational, and accepted medical practice.”).

⁷ FDA, Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs or Cleared Medical Devices (“Guidance on Good Reprint Practices”) at 3 (Jan. 2009), available at <http://www.fda.gov/regulatoryinformation/guidances/ucm125126.htm>.

⁸ J. V. Selby, A.C. Beale, & L. Frank, The Patient-Centered Outcomes Research Institute (PCORI) National Priorities for Research and Initial Research Agenda, 307 J. Am. Med. Ass’n 1583, 1583-1584 (2012).

Science and Technology (PCAST) Report, which recognized as “the most significant change . . . that all healthcare should be organized around the needs and specific characteristics of the patient, not around those of the hospital, doctor’s office, insurance company, or electronic health record vendor.”⁹ Patient-centeredness means that individuals and their caregivers are empowered to make informed health care decisions based on information that they can access as they wish and that they deem relevant, based on their own preferences and values.

This patient focus has fundamentally altered the health care system since PPACA’s enactment, with patients (and their caregivers) changing their expectations about the information available to them about health care interventions. At the same time, formulary committees, payors, and similar entities are occupying an increasingly prominent role in the healthcare delivery system. There, too, PCORI has a central role, with a mandate to fund and promote comparative effectiveness research, including “[s]ystematic reviews” and “observational studies.”¹⁰ PCORI has begun to devise a research agenda to support the development of new data and analysis comparing treatment options. PCORI and other entities are also developing standards for the conduct of real world evidence studies and other non-RCT study designs.

Through its regulatory processes, FDA is responsible for providing much important information about drugs and medical devices, primarily to prescribers through approved labeling. The Agency’s regulatory scheme cannot, however, respond to the full range of information demands that characterize this dynamic system. Manufacturers have “superior access” to product-related information¹¹ and the ability to provide independently derived scientific information about alternative uses of approved products “at the earliest possible time, when it may really make a difference”¹² Yet the current regulatory scheme is not adequate to assure that manufacturers’ role in providing information to key constituencies to support decision making is well-defined and that applicable regulatory constraints are clear. Moreover, recent judicial decisions have brought renewed attention to the significant constitutional limitations on FDA’s power to control the content of truthful and non-misleading health care information provided by manufacturers to prescribers, payors, and patients.

⁹ Executive Office of the President, President’s Council of Advisors on Science and Technology, Realizing the Full Potential of Health Information Technology to Improve Health Care for Americans: The Path Forward, at 24 (Dec. 2010).

¹⁰ See 42 U.S.C. § 1320e(d)(6)(C), (2)(A). PPACA also authorized the Agency for Healthcare Research and Quality (AHRQ) to “disseminate the research findings . . . relevant to comparative clinical effectiveness research.” Id. § 299b-37(a)(1).

¹¹ Wyeth v. Levine, 129 S. Ct. 1187, 1202 (2009).

¹² More Information for Better Patient Care: Hearing of the Senate Comm. on Labor and Human Resources, 104th Cong. 81 (1996) (statement of Dr. Gregory H. Reaman, Director, Medical Specialty Services, Children’s National Medical Center) (“Pharmaceutical and biotechnology companies obviously have an interest in supporting new uses of their products, but they also happen to be in the best position to share information with the physician community at the earliest possible time, when it may really make a difference in treatment options.”); see also 63 Fed. Reg. 64,556, 64,579 (Nov. 20, 1998) (recognizing the “public health gains associated with the earlier dissemination of objective, balanced, and accurate information on important unapproved uses of approved products”) (emphasis added).

B. RECENT JUDICIAL DECISIONS EXPLAIN THE FIRST AND FIFTH AMENDMENT PRINCIPLES THAT CONSTRAIN FDA'S POWER TO REGULATE MANUFACTURER SPEECH

In the past two years the federal courts have decided several cases that implicate the foundations of FDA's regulations and policies governing manufacturer dissemination of information about off-label uses. Sorrell, 131 S. Ct. 2653, Fox II, 132 S. Ct. 2307, and Caronia, 703 F.3d 149, reiterate the First Amendment requirement for the Agency to both adequately justify and appropriately tailor its regulatory regime, and the Fifth Amendment requirement for clarity in the rules governing manufacturer communications. These pivotal judicial decisions, together with prior decisions, establish the following bedrock principles:

First, under the First Amendment, content- and speaker-based restrictions are "presumptively invalid." Sorrell, 131 S. Ct. at 2667 (quoting R.A.V. v. St. Paul, 505 U.S. 377, 382 (1992)). Such restrictions are disfavored because they often embody "the Government's preference for the substance of what the favored speakers have to say (or aversion to what the disfavored speakers have to say)." See Turner Broad. Sys., Inc. v. FCC, 512 U.S. 622, 658 (1994); Sorrell, 131 S. Ct. at 2664 (rejecting regulations motivated by "disagreement with the message [the speech] conveys" (quoting Ward v. Rock Against Racism, 491 U.S. 781, 791 (1989))).

A regime that "disfavors marketing, that is, speech with a particular content" and "specific speakers, namely pharmaceutical manufacturers" is content- and speaker-based. Sorrell, 131 S. Ct. at 2663; see also Caronia, 703 F.3d at 165 ("the 'express purpose and practical effect' of the government's ban on promotion is to 'diminish the effectiveness of [off-label] drug marketing by manufacturers'" (quoting Sorrell, 131 S. Ct. at 2663)). Where a regulatory regime is content- and speaker-based, heightened scrutiny applies. Id. at 2667 ("In the ordinary case it is all but dispositive to conclude that a law is content-based and, in practice, viewpoint-discriminatory.").

Second, the First Amendment disfavors categorical bans on truthful, non-misleading speech about lawful activities. Indeed, "in at least the last 20 years," the Supreme Court has never upheld a restriction on speech that is truthful and advocates lawful purchase. Coleen Klasmeier & Martin H. Redish, Off-Label Prescription Advertising, the FDA and the First Amendment: A Study in the Values of Commercial Speech Protection, 37 Am. J.L. & Med. 315, 341 (2011).

The First Amendment disfavors bans on truthful, non-misleading speech because they often arise from the "paternalistic assumption that the public will use truthful, non-misleading commercial information unwisely." 44 Liquormart, Inc. v. Rhode Island, 517 U.S. 484, 496-97 (1996) (citing Va. Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc., 425 U.S. 748, 770 (1976)); see also Rubin v. Coors Brewing Co., 514 U.S. 476, 497 (1995) (Stevens, J., concurring) ("Any 'interest' in restricting the flow of accurate information because of the perceived danger of that knowledge is anathema to the First Amendment."); Thompson v. Western States Medical Ctr., 535 U.S. 357, 374 (2002) ("We have . . . 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.").

Although an exception exists for truthful, non-misleading speech relating to unlawful activities, that exception is inapplicable here. Prescribing a drug or medical device for

a new use is lawful and a constituent part of the practice of medicine. If the activity to which the speech relates is lawful, and if the speech is not inherently false or misleading, the government must not impose a broad-based ban "simply to spare itself the trouble of distinguishing [permitted] advertising from false or deceptive advertising." Zauderer v. Office of Disciplinary Counsel of the Sup. Ct. of Ohio, 471 U.S. 626, 646 (1985).

Furthermore, and as noted in Caronia, when less speech-restrictive measures (such as disclaimers) can be employed to render speech truthful and non-misleading, those measures should be favored over outright suppression. E.g., id. at 651 n.14 ("[A]ll our discussions of restraints on commercial speech have recommended disclosure requirements as one of the acceptable less restrictive alternatives to actual suppression of speech."); In re R.M.J., 455 U.S. 191, 201 (1982) ("[T]he preferred remedy is more disclosure, rather than less.") (quoting Bates v. State Bar of Ariz., 433 U.S. 350, 375 (1977)); Caronia, 703 F.3d at 168 (suggesting, as an alternative to a ban on promotion of new uses, development of "warning or disclaimer systems") (quoting Klasmeier & Redish, supra). Disclosure systems are preferred because they "open the channels of communication, rather than . . . close them," enabling informed individual choice. See Va. Bd. of Pharmacy, 425 U.S. at 770.

Third, the First and Fifth Amendments require "precision . . . when a statute regulates the content of speech." Reno v. ACLU, 521 U.S. 844, 874 (1997). The Due Process Clause of the Fifth Amendment requires agencies to establish clear rules that give "fair notice of what is prohibited." Fox II, 132 S. Ct. at 2318 (quoting United States v. Williams, 553 U.S. 285, 304 (2008)). The "[s]tandards of permissible statutory vagueness are strict in the area of free expression. . . . Because First Amendment freedoms need breathing space to survive, government may regulate in the area only with narrow specificity." Keyishian v. Bd. of Regents of the U. of N.Y., 385 U.S. 589, 604 (1967) (quoting N.A.A.C.P. v. Button, 371 U.S. 415, 438 (1963); Fox II, 132 S. Ct. at 2317 ("When speech is involved, rigorous adherence to [notice] requirements is necessary to ensure that ambiguity does not chill protected speech."); Marks v. United States, 430 U.S. 188, 196 (1977) (Due Process requirements apply with special force where the government "regulates expression and implicates First Amendment values"). Vagueness in content-based regulation of speech "raises special First Amendment concerns because of its obvious chilling effect . . ." Reno, 521 U.S. at 871-72.

"Problems of vagueness" are "particularly treacherous" where the threat of criminal penalties "may deter those who seek to exercise protected First Amendment rights." Buckley v. Valeo, 424 U.S. 1, 76-77 (1976); see Reno, 521 U.S. at 872 ("The severity of criminal sanctions may well cause speakers to remain silent rather than communicate even arguably unlawful words, ideas, and images"); see also Fox II, 132 S. Ct. at 2318 (holding that fair notice principles operate with greater force "when applied to . . . regulations that touch upon 'sensitive areas of basic First Amendment freedom.'" (quoting Baggett v. Bullitt, 377 U.S. 360, 372 (1964)). Harsh penalties magnify the need for precision because regulated entities will inevitably err on the side of less communication (to the potential detriment of other public-health interests) in order to avoid criminal sanctions.

The application of these three principles to FDA's regulation of manufacturer speech about off-label uses is discussed further below.

C. SPECIFIC MODIFICATIONS RELATED TO ACTIVITIES INVOLVING MEDICAL AND SCIENTIFIC COMMUNICATIONS

1. Interactions with Formulary Committees, Payors, and Similar Entities Responsible for Selecting Products for Managed Care and Analogous Organizations¹³

The July 2011 petition requested that FDA establish a clear safe harbor for manufacturer communication of information about off-label uses and investigational products to payors and similar entities. FDA has yet to address this request, which we renew today and elaborate upon in light of recent federal case law.

As described in the July 2011 petition (p. 10), the extent to which manufacturers may provide such information in accordance with FDA policy is currently unclear. Payors and similar entities play a critical role in the health care delivery system and have distinct informational needs, as we emphasized in our recent comments on the agenda for the CDER Medical Policy Council (Docket No. FDA-2013-N-0206). Payors regularly reimburse for off-label uses, and often follow the federal government's lead—requiring reimbursement if certain off-label uses are medically accepted or listed in compendia¹⁴—which intensifies the need for open lines of communication in this area.

Avenues for manufacturers to share this information are inadequate, however, because relevant statutory and regulatory provisions (i) were enacted decades ago, (ii) focus on the communication of information to prescribers—whose needs and capacity to evaluate data are quite different than payors'—and (iii) have not been clarified or updated to reflect the current landscape. For example, as explained in the July 2011 petition (p. 11), FDA has failed to outline with sufficient clarity the circumstances under which it believes manufacturers may rely on the “scientific exchange” regulation (21 C.F.R. § 312.7) to share truthful information about new uses. Even where FDA's instructions regarding communication of pre-approval information are relatively clear, they are not binding.¹⁵ Similarly, because FDA has not clarified the scope of FDAMA § 114, manufacturers continue to have questions regarding the scope of this statutory provision to communicate health care economic information to payors and analogous entities. See 21 U.S.C. § 352(a). Manufacturers also continue to seek guidance from FDA with respect to the Agency's interpretation of “competent and reliable scientific evidence,” which is the special evidentiary standard that Congress established for health care economic information provided pursuant to FDAMA § 114. The lack of clarity in the current regulatory scheme governing these communications creates significant difficulties for companies in their attempts to comply with government expectations and deprives payor entities and health care professionals of valuable information.

¹³ These entities may include population health decision-makers such as integrated delivery networks (IDNs), treatment guideline and pathway developers, and compendium publishers.

¹⁴ See 42 U.S.C. § 1396r-8(g)(1)(B)(i).

¹⁵ Manufacturers seeking guidance on permissible pre-approval promotion, for example, have little choice but to rely on non-binding letters to industry and similar communications from FDA, the legal significance of which is unclear under FDA's Good Guidance Practices (GGP) regulations, 21 C.F.R. § 10.115; see, e.g., DDMAC, Current Issues and Procedures (Apr. 1994) (outlining FDA regulatory expectations for “Coming Soon” promotion).

Recent case law makes clear that FDA needs to reconsider its approach to the regulation of these communications. Fox II reiterates that the Fifth Amendment requires the government to establish clear standards before restricting speech precisely because of difficulties caused by a vague regulatory framework. See 132 S. Ct. at 2317. FDA's restrictions on manufacturer communications raise significant First Amendment concerns because researchers, payors, counter-detailers, and others have an unfettered ability to discuss and disseminate precisely the type of information that manufacturers may not. Such an approach is subject to heightened scrutiny under Sorrell because it imposes a "content-based" restriction (limiting the type of information that can be shared with payors and other entities engaged in population-level product selection decisions to that which "directly relates to an indication approved" by FDA, 21 U.S.C. § 352(a)) and a "speaker-based" restriction (applying such restrictions only to manufacturers). See Sorrell, 131 S. Ct. at 2660. Under the heightened scrutiny standard, it is virtually certain that FDA's approach would not pass constitutional muster.

2. Dissemination of Third-Party Clinical Practice Guidelines

Academic institutions, leading associations of medical professionals, and even government agencies develop and publish recommendations, in the form of clinical practice guidelines, for physicians and other health care practitioners to use in treating particular health conditions. These guidelines, which are based on up-to-date clinical evidence and data, may sometimes recommend uses of products in ways that vary from FDA-approved labeling.¹⁶ The July 2011 petition (pp. 11-12) proposed that FDA define a safe harbor applicable to the dissemination of these guidelines in certain circumstances.

The Fox II decision emphasizes that, to satisfy constitutional requirements of due process, the government must set forth clear and precise laws in the area of speech regulation before it may take enforcement action based on speech. See 132 S. Ct. at 2320. As explained in the July 2011 petition (pp. 11-12) and in MIWG's comments to FDA's scientific exchange docket (Docket No. FDA-2011-N-0912), FDA has advanced breathtakingly broad interpretations of its own authority over manufacturer speech, and has never taken a position with regard to dissemination of clinical practice guidelines and other information about new uses of drugs and medical devices. As a result, manufacturers must attempt to guess whether and under what circumstances such guidelines may be shared.

Further, manufacturers may seek to avoid liability by limiting or forbidding distribution of clinical practice guidelines even though they contain clinically important information. Indeed, manufacturers tend to under-share truthful and clinically valuable information because of ambiguous regulatory expectations. The chilling effect of the current regulatory scheme, in addition to the disparate impact of the scheme on manufacturers relative to other parties who are permitted to disseminate the guidelines without restriction (e.g., medical societies), directly implicates the First Amendment. See, e.g., Sorrell, 131 S. Ct. at 2660-63; see also Caronia, 703 F.3d at 165. FDA has concluded (albeit in non-binding guidance) that

¹⁶ For example, the Center for Disease Control's Advisory Committee on Immunization Practices develops recommendations for vaccine use in the United States and often recommends use of vaccines in circumstances not set forth in the FDA-approved labeling. See Center for Disease and Prevention Control, "Use of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine for Adults with Immunocompromising Conditions: Recommendations of the Advisory Committee on Immunization Practices (ACIP)," Morbidity and Mortality Weekly Report (Oct. 12, 2012), available at <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6140a4.htm>.

something less than an outright prohibition is appropriate with respect to dissemination of other third-party materials, such as reprints and reference publications.¹⁷ That conclusion should apply equally here.

Indeed, FDA's distinction between communication of clinical practice guidelines and the distribution of reprints of medical and scientific journal articles is completely artificial. FDA has established a limited safe harbor regarding the distribution of medical journal articles and publications discussing new uses of drugs and devices on the ground that FDA "recognize[s] . . . the important public health and policy justification supporting dissemination of truthful and non-misleading medical journal articles and medical or scientific reference publications." The public health rationale supporting reprint dissemination applies with equal force to the distribution of clinical practice guidelines, yet FDA's safe harbor approach does not specifically cover guidelines; in particular, clinical practice guidelines do not clearly fit within the scope of the reprints guidance because they are not typically (1) restricted to adequate and well-controlled trials, certain meta-analyses, and other kinds of data sources permitted under the Good Reprint Practices guidance, or (2) published in peer-reviewed journals.

Moreover, because the government permits and indeed encourages new uses in some instances, any attempt by the government to prohibit manufacturers from disseminating guidelines containing information about off-label uses under the guise of protecting patients or the integrity of the drug approval process would violate the First Amendment and "could inhibit, to the public's detriment, informed and intelligent treatment decisions." Caronia, 703 F.3d at 166; see also id. ("As off-label drug use itself is not prohibited, it does not follow that prohibiting the truthful promotion of off-label drug use by a particular class of speakers would directly further the government's goals of preserving the efficacy and integrity of the FDA's drug approval process and reducing patient exposure to unsafe and ineffective drugs.") (citing Sorrell, 131 S. Ct. at 2668-69).

3. Responses to Unsolicited Requests and Scientific Exchange

As noted above, FDA has taken initial steps to address two of the requests set forth in the July 2011 petition: (1) that the Agency clarify the contours of the safe harbor for manufacturer responses to unsolicited requests; and (2) that it establish clear boundaries within which manufacturer communications constitute scientific exchange. Comments of certain MIWG member companies on FDA's draft guidance on responses to unsolicited requests and the MIWG's comments in response to FDA's December 2011 notice on scientific exchange¹⁸ are found in their respective public dockets, and we will not reiterate them here.

Sorrell and Caronia directly affect the draft guidance on unsolicited requests and the scientific exchange notice, because both purport to distinguish permissible from impermissible speech based on content, speaker, and audience. FDA's draft guidance on unsolicited requests, for example, indicates that manufacturers should censor internet responses on the basis that consumers, rather than physicians, might view them.¹⁹ Additionally, the draft guidance distinguishes between public and non-public responses to unsolicited requests and suggests that it would be unlawful for a manufacturer to respond substantively to

¹⁷ See FDA, Guidance on Good Reprint Practices, supra n. 7.

¹⁸ 76 Fed. Reg. 82,303 (Dec. 30, 2011) (notice of availability of draft guidance); 76 Fed. Reg. 81,508 (Dec. 28, 2011) (scientific exchange notice).

¹⁹ FDA, Draft Guidance on Unsolicited Requests, supra n. 4, at 13.

unsolicited questions regarding new uses received in a public forum. Similarly, questions set forth by FDA in the notice on scientific exchange suggest that the Agency may be considering categorizing manufacturer speech according to the type of forum in which it occurs, and the identity of the speakers or listeners.²⁰ As applied to truthful, non-misleading speech about off-label uses, such content- and speaker-based distinctions run afoul of the First Amendment as most recently explained in Sorrell and Caronia and require close reexamination by the Agency.²¹

D. MODIFICATIONS TO THE FOUNDATIONS OF THE REGULATORY SCHEME

Part II.B sets forth key constitutional principles reflected in Sorrell, Fox II, and Caronia, and in the broader body of case law arising in the First and Fifth Amendment contexts. These principles must inform not only FDA policies on the four specific forms of manufacturer communication addressed in the July 2011 petition, but also the foundations of FDA's regulatory scheme. Below we provide a non-exhaustive list of suggestions for the Agency to consider as it examines the implications of the case law on the most fundamental aspects of the Agency's oversight of manufacturer communications. As noted above, we believe that, although the current regulatory scheme presents grave constitutional difficulties, FDA can better respect constitutional limitations, while also fulfilling its public health mission, by interpreting the scope of its regulatory authority more consistently with the FDCA.

This authority is defined with reference to the "labeling" and "advertising" provisions of the FDCA, and to the regulatory definition of "intended use" in 21 C.F.R. §§ 201.128 (drugs) and 801.4 (devices). In the past, FDA has interpreted these provisions broadly to include virtually any manufacturer activity that involves the dissemination of information about a drug or medical device.²² Where FDA has allowed manufacturers to provide off-label use information, the Agency has done so on the premise that it is exercising its discretion not to apply the FDCA to these activities, and has reserved the right to proceed against a manufacturer in any specific case.²³ Moreover, FDA has not readily acknowledged that the FDCA imposes any clear limitation on the scope of the Agency's authority over manufacturer speech. Indeed, FDA officials have rejected pleas for greater clarity, or even a process for manufacturers to obtain FDA's advice on proposed activities, claiming that to do either would be anathema to effective regulation.²⁴

²⁰ See id. at 81,509.

²¹ See, e.g., Caronia, 703 F.3d at 164-165 (applying heightened scrutiny due to the content-based distinction between on- and "off-label" speech and the speaker-based distinction between pharmaceutical manufacturers and other individuals such as physicians and academics).

²² See, e.g., 62 Fed. Reg. 64,074, 64,080 (Dec. 3, 1997) ("In order to protect and promote the public health, Congress granted FDA broad statutory authority to ensure that promotional activities (labeling and advertising) for drugs and devices are truthful and not misleading.").

²³ See, e.g., FDA, Guidance on Good Reprint Practices, supra n. 7, at 6 ("[I]f a manufacturer follows the recommendations described in Section IV of this guidance, FDA does not intend to consider the distribution of such medical and scientific information in accordance with the recommendations in this guidance as establishing intent that the product be used for an unapproved new use.") (emphasis added).

²⁴ Members of the MIWG submitted comments to the transparency docket asking FDA to revive the advisory opinion process to ameliorate the lack of clarity in the regulatory environment. FDA declined that request on the ground that doing so "may place inappropriate restrictions on FDA's ability to respond to emerging issues to best protect and promote the public health." See Transparency Task Force, DHHS,

FDA could assure that the regulatory scheme better aligns with the FDCA and with First and Fifth Amendment limitations by providing clear interpretations of these key definitions that are consistent with the statute. As noted below, “labeling” does not include every type of material that is textually related to a drug or device, but is limited by statute to “written, printed, or graphic matter” that “accompanies” the product in a particular way. “Advertising” is similarly limited by the statutory text and structure. Finally, FDA could make certain that the regulatory scheme is more consistent with statutory limitations and constitutional principles by adopting a definition of “intended use” in its regulations that is clearer and does not impinge on manufacturers’ entitlement to engage in “scientific exchange” or other forms of truthful, non-misleading speech.

1. The Scope of “Labeling”

Section 201(m) of the FDCA defines labeling to include written, printed, or graphic matter “accompanying” a product. 21 U.S.C. § 321(m). When it was enacted, the term “labeling” was understood to mean the material that is inside the package of a product. See, e.g., S. Rep. No. 74-361, at 4-5 (1935) (“differentiation between label and labeling is necessary because the declaration of certain facts . . . should . . . appear on the principal label or labels where they can be easily observed, rather than on side panels of the labeling or in circulars within the package where they may escape notice”) (emphasis added). This made sense, because the case law at the time also reflected the “package insert” definition of “labeling.” 7 Cases of Eckman’s Alterative v. United States, 239 U.S. 510, 517 (1916).

In 1948, in United States v. Korde, the Supreme Court held that a manufacturer cannot evade the Act’s “labeling” requirements simply by sending drugs and “literature” in two separate shipments. See 335 U.S. 345, 348-351 (1948) (“The question whether the separate shipment of the literature saved the drugs from being misbranded within the meaning of the Act presents the main issue in the case. . . . [W]e conclude that the phrase ‘accompanying such article’ is not restricted to labels that are on or in the article or package that is transported.”).

The Court held that materials shipped separately can constitute “labeling”—regardless of physical proximity—when they “perform] the function of labeling.” Id. at 350 (emphasis added). The Court provided the following guidance in determining whether a “display of . . . matter” performs the “function” of labeling:

- “Nowhere else [is] the purchaser advised how to use [the article].” Id. at 348.
- “It constitute[s] an essential supplement to the label attached to the package.” Id.
- “[I]t supplements or explains [the product], in the manner that a committee report of the Congress accompanies a bill.” Id. at 350.
- The materials and products are “interdependent; they [are] parts of an integrated distribution program.” Id.

These descriptions of the “function” of labeling make clear that not all “written, printed, or graphic matter” that merely mentions a product qualifies as “labeling.” As we have explained in

prior comments (Docket No. FDA-2011-N-0912), labeling performs the unique role of “supplement[ing] and explain[ing]” a product in order to guide its use.

Clarifying the “labeling” definition consistent with the factors above would both give clearer meaning to Section 201(m) and make it more consistent with the First and Fifth Amendments, with the relevant statutory language, and with Kordel. A properly constrained definition of “labeling” would enable manufacturers to understand in advance which of their “written, printed, or graphic” communications would be subject to regulation by FDA, ultimately opening up new channels of truthful, non-misleading communication as envisioned by the First Amendment.

To achieve the objective of establishing a clear definition of “labeling” that is consistent with the statutory text as explicated by the Supreme Court in Kordel, FDA would not have to amend its existing regulations defining “labeling.” Two regulatory provisions are relevant:

- 21 C.F.R. § 1.3(a), the general regulation defining “labeling” for all FDA-regulated products, states: “Labeling includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce”; and
- 21 C.F.R. § 202.1(l)(2), the prescription drug advertising regulation defining “labeling,” sets forth an extensive list of items that are deemed to be within the scope of the “labeling” definition.

In the past, FDA has cited § 202.1(l)(2) as though it functioned as a regulatory interpretation of the statutory definition of “labeling” in Section 201(m) of the FDCA.²⁵ As a result of those and other statements, manufacturers believed that virtually any type of written communication in which they engaged could be regulated as promotional “labeling” by FDA. Such communications could not include information about new uses because of the statutory prohibitions governing “labeling.”

Recently, however, the government has explained that § 202.1(l)(2) does not define “labeling,” but rather operates to exclude the listed communications from the definition of “advertising” in the FDCA:

Section 202.1(l)(2) was issued pursuant to 21 U.S.C. § 352(n), which governs prescription drug advertising. By its terms, Section 352(n) excludes “any printed matter which the Secretary determines to be labeling” Section 202.1(l)(2), which lists items that “are hereby determined to be labeling,” was issued to implement this exclusion. In keeping with the terms of Section 352(n), its purpose is to limit the domain of the Act’s prescription drug advertising requirements, by making clear what kinds of materials are not subject to those requirements. It was never meant to suggest that the items in the list will be regulated as labeling without regard to Kordel’s construction of

²⁵ See, e.g., FDA, Draft Guidance for Industry: Presenting Risk Information in Prescription Drug and Medical Device Promotion (May 2009), available at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM155480.pdf.

“accompanying,” and it has not been applied by FDA in that manner.

Def.’s Reply in Supp. of Mot. to Dismiss or Summ. J. at 22-23, Allergan, Inc. v. United States, Civ. Action No. 09-1879 (D.D.C. Mar. 29, 2010). To assure that its regulations are consistent with Section 201(m) as explicated in the case law, the Agency should both (1) engage in notice-and-comment rulemaking to remove § 202.1(l)(2) from the rules, and (2) confirm that “labeling” in the prescription drug and medical device context is defined by 21 C.F.R. § 1.3(a), which is more consistent with the statutory language and with Kordel.

2. The Scope of “Advertisements”

Sections 502(n) and (r) of the FDCA grant the agency authority over prescription-drug and restricted-device advertising, respectively. As we have explained in prior comments (Docket No. FDA-2011-N-0912), the scope of the “advertising” definition is limited. According to FDA regulations, advertising refers to communications that are “published” or “broadcast”—that is, paid placements in third-party media. 21 C.F.R. § 202.1(l)(1). Properly construed, the FDCA provisions delineating FDA’s authority over advertising—or, for that matter, labeling—do not reach scientific exchange.

FDA should take steps to clarify the definition of advertising, and limit its application of the detailed regulations in Part 202 to communications that properly fall within that definition. Clarification would serve the Fifth Amendment interest in clear and precise rules. It would also help align FDA’s regulatory regime with the First Amendment, because it would cabin the speech-suppressing effect of FDA’s advertising regulations and leave open alternative channels of truthful, non-misleading manufacturer communication about off-label uses.

To achieve the objective of clarifying the definition of advertising and preserving scientific exchange, FDA could establish clear lines of demarcation between communications that are beyond the scope of the Agency’s advertising authorities, by providing a clear definition of “scientific exchange” that makes the contours of that safe harbor easier to discern. As indicated in our comments in response to the Agency’s December 28, 2011 notice on “scientific exchange,” the 1987 preamble language set forth in the July 2011 citizen petition and reproduced in the December 28 notice represents a sound approach to defining scientific exchange.²⁶

3. The Scope of “Intended Use”

The MIWG’s third suggestion relates to 21 C.F.R. §§ 201.128 & 801.4, parallel provisions of FDA’s drug and device labeling regulations that have contributed to confusion among manufacturers and federal officials for more than five decades. The meaning of

²⁶ 52 Fed. Reg. 19,466, 19,475 (May 22, 1987). The language recommends that manufacturers making statements about investigational new drugs (1) make clear that the drug is investigational, (2) make no claims that the drug has been proven to be safe or effective, and (3) assure that their statements are truthful and non-misleading “when measured against available information on the drug . . . as set forth in materials such as investigators’ brochures” It would be necessary, in adopting the approach reflected in this language, to explain the meaning of “claims” in the second criterion, and extend the approach reflected in the language so that it also explicitly covers new uses (in addition to investigational products) and medical devices.

"intended use" under these regulatory provisions, which implement Section 502(f)(1) of the FDCA, 21 U.S.C. § 351(f)(1), is unclear, for the following reasons:

- a) *FDA has not explained when statements that do not pertain to an entirely new disease state or health condition create a "new use."*

The regulatory definitions in 21 C.F.R. §§ 201.128 and 801.4 refer only to a product's "purpose," and to "conditions, purposes, or uses other than the ones for which" the product is offered. In preamble commentary and guidance, FDA has advanced differing interpretations, sometimes asserting that manufacturer communications are "off-label" and raise compliance concerns if they "contain effectiveness rates, data, analyses, uses, regimens, or other information that is different from the approved labeling," 60 Fed. Reg. 63,384, 63,384 (Dec. 8, 1995), while other times asserting that manufacturers are engaging in "off-label" communication if their statements relate to "a use that is not included in the approved labeling of an approved drug or device or a use that is not included in the statement of intended use for a cleared device," *e.g.*, 63 Fed. Reg. 31,143, 31,145 (June 8, 1998).

In the most expansive statement from FDA of which we are aware, the Agency (in response to industry comments) conceded that not every conceivable departure from approved labeling was included in the "off-label" category, but failed to explain when an "out of label" use constituted an "off-label" use. 63 Fed. Reg. 64,556, 64,559 (Nov. 20, 1998).²⁷ The most FDA has said is that a use is "new" if FDA would expect the manufacturer to submit a supplemental application to add it to approved labeling. *See* 63 Fed. Reg. at 31,145 ("A new use is one that would require approval or clearance of a supplemental application in order for it to be included in the product labeling").

FDA's own guidance documents and other statements have recognized the ability to rely on data from registration trials to conclude that an unlabeled use is effective. This is often the situation with respect to patient subpopulations, among other scenarios.²⁸ As a senior FDA official acknowledged in a 2007 interview, the term "off-label use" is used differently by different people. In the pediatric context, "There's no question that people have thought the widespread use in children is sort of close to an off-label use, but it seems not so clear" ²⁹ Although an arguably widespread view holds that use in a patient subgroup, such as pediatrics, is necessarily off-label, in fact such use is often supported by data described in approved labeling and is, therefore, "on-label."

²⁷ FDA had stated that the "new use" definition was broad enough to encompass, in any given case, at least the following: "A completely different indication; modification of an existing indication to include a new dose, a new dosing schedule, a new route of administration, a different duration of usage, a new age group (e.g., unique safety or effectiveness in the elderly), another patient subgroup not explicitly identified in the current labeling, a different stage of the disease, a different intended outcome (e.g., long-term survival benefit, improved quality of life, disease amelioration), effectiveness for a sign or symptom of the disease not in the current labeling; and comparative claims to other agents for treatment of the same condition." 63 Fed. Reg. at 31,145.

²⁸ FDA acknowledged this precise point in response to industry comments on the proposed Part 99 regulations. 63 Fed. Reg. at 64,559.

²⁹ Frontline, *The Medicated Child: Interview with Robert Temple* (posted Jan. 8, 2008), [available at http://www.pbs.org/wgbh/pages/frontline/medicatedchild/interviews/temple.html](http://www.pbs.org/wgbh/pages/frontline/medicatedchild/interviews/temple.html).

Manufacturers therefore are left to speculate as to whether their communications about departures from approved labeling could give rise to FDCA liability, and the lack of meaningful a priori definitions or interpretative guidance from FDA chills truthful and non-misleading manufacturer speech about new uses of approved products.

- b) *Ambiguity exists not only with respect to the types of variations from approved labeling that can create a new use, but also in the types of evidence on which FDA can rely in asserting that a manufacturer has "intended" such a use under the FDCA.*

It remains unclear whether a new use can be created under Section 502(f)(1) in the absence of a manufacturer's claims as to that use. Under the current regulatory language, despite the general rule that intended use is based on the manufacturer's "expressions," a new intended use can also be created when a drug or medical device "is to be used" off-label. 21 C.F.R. §§ 201.128 & 801.4. Under the latter theory, a manufacturer would be in violation of the misbranding provisions of FDCA, despite the absence of promotion of a new use, if the manufacturer merely was on constructive notice of the new use (in the terms of the regulations, if the manufacturer had "knowledge of facts that would give him notice").

Problems with this interpretation were identified from the moment of its inception more than sixty years ago. Manufacturers submitted comments on the proposed rule objecting to the possibility of liability based solely on a known new use. They objected, as well, to the asserted obligation to seek approval for a new use that they did not recommend. See Letter from John L. Hammer, Jr., Vice President, Smith, Kline & French Laboratories to Hearing Clerk, Federal Security Agency (Mar. 4, 1952) (if manufacturer's "market research department learns that 20% of the purchasers use the preparation as a sedative . . . [and] he inserts in his label directions for use as a sedative . . . he is forced into the position of recommending his product for a use of which he heartily disapproves and for which his drug may be largely ineffective").

Doubtless because of the potential consequences of so unbounded an interpretation, FDA "has repeatedly stated that it may only regulate claimed uses of drugs, not all foreseeable or actual uses."³⁰ Prosecutors have nevertheless sought to invoke FDA's regulatory definitions of intended use to support FDCA liability based on a manufacturer's mere knowledge that its product is being used off-label.³¹ Manufacturers therefore have difficulty in evaluating a wide range of proposed business practices that clearly should be lawful, but could be regarded by prosecutors as evidence in a misbranding action under the FDCA because they involve off-label uses that are in no way promoted but are actually or constructively known to them. Two examples of the scenarios commonly confronted by manufacturers illustrate the point:

³⁰ See Ass'n of Am. Physicians & Surgeons v. FDA, 226 F. Supp. 2d 204, 217-18 (D.D.C. 2002) (stating that "even the FDA has repeatedly stated that it may only regulate claimed uses of drugs, not all foreseeable or actual uses"). Similarly, in defending its regulatory scheme from First Amendment challenge, FDA was forced to concede that "not all speech or actions by a manufacturer regarding an unapproved use is [sic] taken by FDA to be evidence of intended use." Mem. in Supp. of Mot. to Dismiss or for Summ. J. at 10, Allergan v. United States, Civ. Action No. 09-01879 (D.D.C. filed Dec. 11, 2009).

³¹ In investigating Par Pharmaceuticals, the Government asserted that "[a] manufacturer's knowledge that a drug may be prescribed for an unapproved use does not lead, by itself, to a conclusion that the unapproved use is intended," but "[k]nowledge that a drug is being offered and used for unapproved purposes is one of the circumstances that may be taken into account" See Defs.' Mem. In Supp. of Mot. To Dismiss or for Summ. J. at 8, 29, Par Pharmaceutical, Inc. v. United States, Civ. Action No. 11-01820 (D.D.C. filed Jan. 11, 2012) (emphasis added).

- A purchaser or payor negotiates discount arrangements with manufacturers, according to which a reduced price is honored for a product if certain utilization benchmarks are met. If reaching the benchmark quantity entails some off-label use of the product, the manufacturer may be forced to abandon the contracting arrangement, even though the off-label use is not the result of manufacturer promotion, and may even represent the standard of care.
- A manufacturer's primary-care drug product is indicated broadly for the treatment of a disease state that occurs across all patient subgroups, but lacks a pediatric indication. The manufacturer must give direction to field sales personnel regarding the physician practices on which it is permissible to call for promotional purposes, including sampling. The manufacturer decides that it must prohibit its sales representatives from calling on practitioners that treat pediatric patients, among others, because of the risk of government allegations that sampling the drug to these practitioners could give rise to an inference that the manufacturer "intends" for the drug to be used off-label.

In these and countless other situations, manufacturers self-censor because FDA has not provided adequate up-front guidance as to the scope of the "intended use" concept.

Read correctly, §§ 201.128 and 801.4 do not support liability in the absence of claims. The regulations, in their respective fourth sentences, refer to the article being "offered and used" off-label. As a result, no new intended use should arise from actual use in the absence of "an offer"—that is, a manufacturer's promotion of the use. Moreover, it is impossible for manufacturers to avoid knowledge of the actual, off-label uses to which their products are being put. Nevertheless, without the definitional clarity, the only recourse a manufacturer has to manage its potential liability based on the knowledge-based intended use theory would be to try and stamp out off-label uses—interference with medical practice that conflicts with FDA policy and could undermine the public health.

Other novel theories of intended use are similarly invalid. Because, as the text of FDA's regulations makes clear, "intended use" is an objective rather than a subjective standard, internal company documents reflecting a subjective desire that a product be used off-label cannot be used as evidence of a misbranding or other FDCA violation. Indeed, "courts 'have always read . . . 'intended' to refer to specific marketing representations." Amer. Health Prods. Co. v. Hayes, 574 F. Supp. 1498, 1505 (S.D.N.Y. 1983) (emphasis added) (citations omitted).³² Consequently, intended use cannot be determined according to just any source.³³ Rather,

³² Courts have also made clear that statements must be disseminated to the public to create new intended uses. See United States v. Articles of Drug for Veterinary Use, 50 F.3d 497, 500 (8th Cir. 1995) (holding that FDA must demonstrate that the materials in question are promotional in nature, actually distributed to customers, and relied on by those customers to establish an intended use). Thus, intended use not only excludes "subjective intent," but also requires evidence of statements that were actually made to the public.

³³ In the past, to support a broad interpretation of intended use, FDA has invoked case law stating that intended use may be based on statements in labeling, advertising, or "any other relevant source." E.g., Letter from Margaret M. Dotzel, Assoc. Commissioner for Policy, FDA to Daniel J. Popeo & Richard A. Samp, Wash. Legal Found., at 4 (Jan. 28, 2002). Such reliance is misplaced, because courts have invoked the "other relevant source" language, which originated in Hanson v. United States, 417 F. Supp. 30 (D. Minn. 1976), aff'd, 540 F.2d 947 (8th Cir. 1976) (per curiam), exclusively in cases in which there were manufacturer promotional claims. See United States v. Article . . . "Sudden Change", 409 F.2d 734, 739 (2d Cir. 1969) (advertisements); United States v. Millipax, Inc., 313 F.2d 152 (7th Cir. 1963) (letters

intended use is created by a manufacturer's promotional claims, as the relevant regulatory text and case law make clear.

The MIWG believes that FDA should provide a clear definition of "intended use" to enable manufacturers to distinguish permitted from prohibited speech. It is simply not enough for FDA to take the position that the Agency knows an off-label use when it sees one, or that manufacturers should know, despite the absence of relevant FDA guidance, whether a departure from approved labeling constitutes an "off-label use." The MIWG believes that, under the FDCA and in order to respect constitutional limitations, FDA should define "intended use" to mean "objective" evidence in the form of explicit promotional claims, whether they appear in communications that themselves qualify as "labeling" or "advertising" or in oral statements by sales representatives. The intended use regulations should include, as well, a cross-reference to the revised and clarified definitions of scientific exchange in 21 C.F.R. §§ 312.7(a) & 812.7(a) (as described in our comments submitted in response to the Agency's December 28, 2011, notice), so that manufacturer participation in such communications is not chilled by the legitimate fear that the government will assert that those non-promotional communications are properly regarded as "evidence of intent" in a misbranding action.

E. CONCLUSION

For many years, ambiguity in the regulatory scheme governing dissemination of information about off-label uses has required manufacturers to expend substantial time and resources attempting to discern the contours of relevant safe harbors and to conform their practices to inchoate regulatory expectations. FDA has in the past announced various initiatives to bring clarity to the regulatory scheme, but many times, the Agency has abandoned or delayed its efforts—leaving industry to operate without clear, predictable rules.³⁴ The chilling effect of the lack of clarity has constitutional dimensions that have been the subject of important developments in the case law over the past two years.

Sorrell, Fox II, and Caronia necessitate a careful reexamination of FDA's regulatory scheme for manufacturer dissemination of information about off-label uses. Clarity and precision in the law are required, and particularly "when speech is involved, rigorous adherence to those requirements is necessary to ensure that ambiguity does not chill protected speech." Fox II, 132 S. Ct. at 2317. In addition, a comprehensive review of the regulatory scheme governing new-use communications is necessary to satisfy FDA's constitutional obligations, with appropriate modifications to assure that the regulations are not applied beyond

and oral representations), cert. denied, 373 U.S. 903 (1963); Nature Food Centres, Inc. v. United States, 310 F.2d 67 (1st Cir. 1962) (speeches at public lecture hall), cert. denied, 371 U.S. 968 (1963); V.E. Irons v. United States, 244 F.2d 34 (1st Cir. 1957) (statements of authorized distributor), cert. denied, 354 U.S. 923 (1957); United States v. Articles of Drug . . . Foods Plus, Inc., 239 F. Supp. 465 (D.N.J. 1965) (radio broadcast), aff'd, 362 F.2d 923 (3d Cir. 1966); see also Lingle v. Chevron U.S.A. Inc., 544 U.S. 528, 531 (2005) ("On occasion, a would-be doctrinal rule or test finds its way into our case law through simple repetition of a phrase—however fortuitously coined.").

³⁴ In 2002, FDA solicited comment on issues related to the First Amendment. See 67 Fed. Reg. 34,942 (May 16, 2002). The Agency held public meetings in 1996 and 2009 to address product promotion on the internet and through social media but has yet to make adequate progress in providing even guidance on these issues. See 61 Fed. Reg. 48,707 (Sept. 16, 1996); see also 74 Fed. Reg. 48,083 (Sept. 21, 2009).

the limitations imposed by Congress in the FDCA, and are properly circumscribed to avoid chilling valuable manufacturer speech.

For these reasons, we request that FDA open a public docket to address manufacturer communications with payors and similar entities and the dissemination of clinical practice guidelines, as well as reevaluate its approach to unsolicited requests and scientific exchange. We also request that FDA commence a process with broad stakeholder involvement to ensure that the very foundations of FDA's regulatory scheme—including the definitions of labeling, advertising, and intended use—respect constitutional and statutory limitations.

III. OTHER REQUIRED INFORMATION FOR FILING OF CITIZEN PETITION

A. ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusion under 21 C.F.R. § 25.31.

B. ECONOMIC IMPACT

Pursuant to 21 C.F.R. § 10.30(b), an economic impact statement will be submitted upon request of the Commissioner.

C. CERTIFICATION

The undersigned certify that, to the best of their knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Respectfully submitted,

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