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Via Electronic Submission

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Draft Guidance for Industry: "Distributing Scientific and Medical Publications on Unapproved New Uses – Recommended Practices" (Docket No. FDA–2008–D–0053)

The Medical Information Working Group ("MIWG") appreciates the opportunity to provide the United States Food and Drug Administration ("FDA") with comments on the draft guidance, "Distributing Scientific and Medical Publications on Unapproved New Uses – Recommended Practices" ("*Draft Guidance*"). The MIWG is a coalition of major manufacturers of prescription drugs and medical devices (including biological products) that 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.[1]

The MIWG acknowledges FDA's ongoing efforts to address the issues raised in the citizen petitions our members filed with the agency in 2011 and 2013.[2] In particular, we recognize that FDA has responded to those petitions in part by establishing a public docket to solicit input on the concept of scientific exchange,[3] issuing draft recommendations for manufacturers to consider when responding to unsolicited requests for off-label information,[4] and clarifying in the above-captioned *Draft Guidance* that manufacturers may disseminate third-party clinical practice guidelines ("CPGs") that discuss new uses for approved/cleared products.

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[1] Members of the MIWG include: Allergan, Inc.; Amgen 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] Citizen Petition, Docket No. FDA-2013-P-1079 (Sept. 3, 2013); Citizen Petition, Docket No. FDA-2011-P-0512 (July 5, 2011).

[3] 76 Fed. Reg. 81,508 (Dec. 28, 2011); Docket No. FDA-2011-N-0912. *See also* Revised Draft Guidance for Industry on Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices; Availability, 79 Fed. Reg. 11,793, 11,793 (Mar. 3, 2014) [*hereinafter* "Draft Guidance Notice of Availability"].

[4] 76 Fed. Reg. 82,303 (Dec. 30, 2011); Docket No. FDA-2011-D-0868; FDA, Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices (Draft), (Dec. 2011). *See also* Draft Guidance Notice of Availability at 11,794.

We further recognize that FDA states that it is considering draft guidance on industry interactions with formulary committees and payers.[5] We respectfully request that FDA complete its policy development in these areas, and when doing so, be mindful of the public health, statutory limitations, and recent First and Fifth Amendment case law. Additionally, we reiterate the request from our 2013 citizen petition that FDA comprehensively review and modify as necessary its entire regulatory approach to manufacturer communications in light of those considerations.[6] We recognize that FDA states that it is engaging in such a review, and we ask that the agency do so in an expeditious manner.

With respect to the *Draft Guidance*, we support the agency's endeavor to provide additional clarity regarding the means by which manufacturers may distribute truthful, non-misleading information about new uses of approved/cleared products. We are nevertheless concerned that the *Draft Guidance* understates the clinical value of new-use information, is inconsistent with statutory and constitutional limitations on FDA's authority, and raises serious concerns about manufacturers' ability to comply with the recommendations. Our comments to the *Draft Guidance* can be summarized as follows:

- Part I addresses the public health importance of off-label use information and requests that FDA more clearly acknowledge its value when finalizing the guidance.

- Part II describes the statutory and constitutional framework governing FDA's limitations on manufacturer speech. In particular, we request that FDA clarify that materials disseminated under the *Draft Guidance* do not constitute labeling for purposes of the Federal Food, Drug, and Cosmetic Act ("FDCA"). Additionally, we highlight several instances in which the recommendations contained in the *Draft Guidance* do not appear to pass constitutional muster, and we ask that FDA reconsider them in light of recent case law.

- Part III sets forth our concerns with respect to certain recommendations proposed in the *Draft Guidance*. In particular:
    - We discuss certain of the recommendations applicable to scientific and medical publications covered by the *Draft Guidance* and offer suggestions for modifying the recommendations relating to (i) the false-or-misleading prohibition; (ii) the ban on publications edited or significantly influenced by the manufacturer; (iii) the disclosure of the nature and amount of an author's financial interest in the manufacturer; (iv) manufacturer disclosure of all significant risks associated with the use of the product that are not referenced in the disseminated material; and (v) the characterization of information that is "promotional in nature."
    - We ask FDA to reconsider its recommendation that journal articles distributed under the *Draft Guidance* be limited to those reporting on adequate and well-controlled studies, and we urge the agency to restore drug manufacturers' ability to disseminate

[5] *See* Draft Guidance Notice of Availability at 11,794.
[6] *Sorrell v. IMS Health, Inc.*, 131 S. Ct. 2653 (2011); *FCC v. Fox Television Stations*, 132 S. Ct. 2307 (2012) (Fox II); *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012)).

historically controlled studies, meta-analyses, and pharmacodynamic ("PD") and pharmacokinetic ("PK") studies.

- We describe our concerns with the recommendation that reference texts and CPGs be based on a "systematic review of the evidence" and also with the agency's reliance on the Institute of Medicine's ("IOM") "trustworthiness" criteria for CPGs. We further ask the agency for additional clarity regarding two other recommendations applicable to the dissemination of reference texts.

I. The Public Health Benefits from Increased Distribution of New-Use Information

FDA acknowledges in the *Draft Guidance* that there is "value to health care professionals of truthful and non-misleading scientific or medical publications on unapproved uses."[7] The MIWG fully concurs with this statement, which rests on the fundamental principle that a "health care professional can generally choose to use or prescribe an approved or cleared medical product for an unapproved use, if the off-label use is appropriate based on his or her judgment."[8] For health care professionals to best exercise their professional judgment, and for the public health to be protected, it is critical that health care professionals have access to up-to-date medical information about a product, including truthful and non-misleading information on off-label uses.

FDA goes to great lengths in the *Draft Guidance* to emphasize the importance of premarket review, describing the dangers of clinical decision-making based on anecdotal or poor quality evidence and citing decades-old examples of drugs whose preliminary evidence of safety or effectiveness was not ultimately borne out by the clinical data.[9] We do not dispute the value of premarket review. Premarket review for each clinically appropriate use of approved drugs is not always practical, though, and for many diseases, off-label treatments are the only therapies available. For others, "a drug given off-label may have been proven to be safer and more beneficial than any drug labeled for that disease."[10] Indeed, in the "Purpose" section of the 2009 *Reprints Guidance*, FDA emphasized that off-label use is a lawful,[11] well-established,[12] and

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[7] FDA, Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses – Recommended Practices (Draft), 6-7 (Feb. 2014) [*hereinafter* "Draft Guidance"].

[8] *Id. See also, e.g.*, 37 Fed. Reg. 16,503, 16,504 (Aug. 15, 1972) ("The physician is then responsible for making the final judgment as to which, if any, of the available drugs his patient will receive in the light of the information contained in their labeling and other adequate scientific data available to him.").

[9] Draft Guidance at 2.

[10] *See* Bryan A. Liang and Tim Mackey, Reforming Off-Label Promotion to Enhance Orphan Disease Treatment, 327 Science 273, 273-74 (Jan. 15, 2010); Off-Label Drug Use and FDA Review of Supplemental Drug Applications: Hearing Before the Subcomm. on Human Resources and Intergovernmental Relations of the H. Comm. on Government Reform and Oversight, 104th Cong. 12 (1996) (statement of Sarah F. Jaggar, Dir. of Health Services Quality and Public Health Issues, Health, Education, and Human Services Division, GAO).

[11] *See* 21 U.S.C. § 396 ("Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease . . . ."); *Caronia*, 703 F.3d at 165 ("[P]romoting off-label drug use concerns lawful activity (off-label drug use) . . . ."); 21 C.F.R. § 312.2(d) (exemption from FDA regulations for "the use in the practice of medicine for an unlabeled indication of a new drug product approved" by the agency); Proposed New Drug, Antibiotic, and Biologic Drug Product Regulations, 48 Fed. Reg. 26,720, 26,733 (June 9, 1983) ("Once a drug product has been approved for marketing, a physician may, in treating patients, prescribe the drug for uses not included in the drug's approved labeling.").

important aspect of quality medical care.[13] In the *Draft Guidance*, however, FDA characterizes the safe harbor for disseminating scientific and medical communications as a "narrow" one,[14] appearing to take the position that such information is generally prohibited and disfavored even when critical to supplement to the premarket review process. FDA's position in the *Draft Guidance* is inconsistent with both good clinical practice and constitutional principles. In addition, we are unaware of any change in the period between the issuance of the 2009 *Reprints Guidance* and the *Draft Guidance* that would justify this shift. The MIWG believes that the language used in the 2009 *Reprints Guidance* more clearly reflects the public health importance of off-label use information and was consistent with the Constitution. We request that FDA revert to such language before finalizing the *Draft Guidance*.

II. The Framework Underpinning the *Draft Guidance*

A. The Regulation of "Labeling"

The *Draft Guidance* takes as a given that FDA has the authority to regulate, indeed prohibit, the dissemination of scientific and medical materials because such re-publications of others' speech constitutes labeling under the FDCA. The FDCA defines "labeling" to mean "written, printed, or graphic matter" upon the article or "any of its containers or wrappers," or "accompanying such article."[15] The Supreme Court in *Kordel v. United States*, the case on which FDA relies on for its labeling authority, addressed whether written material could "accompany" a drug, and thus qualify as labeling, even when it was distributed separately from the package.[16] The Court held that written materials comprise "labeling" when they: (1) have the same origin as the drug; (2) have the same destination; (3) are designed for use in the sale and distribution of the drug; and (4) have a "textual relationship" or "constitute an *essential* supplement" to the label.[17] As subsequent decisions have explained, "labeling does not include every writing which bears some relation to the product. There is a line to be drawn, and, if the statutory purpose is to be served, it must be drawn in terms of the function served by the writing."[18] Properly construed,[19] FDA's "labeling" authority does not reach manufacturer

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[12] Donna T. Chen et al., U.S. Physician Knowledge of the FDA-Approved Indications and Evidence Base for Commonly Prescribed Drugs: Results of a National Survey, 18 Pharmacoepidemiology & Drug Safety 1094 (2009) (footnotes omitted) (Off-label prescribing is "common, can be a source of innovation, and in some settings may represent the standard of care.").

[13] 2009 Reprints Guidance, at 3 ("Once a drug or medical device has been approved or cleared by FDA, generally, healthcare professionals may lawfully use or prescribe that product for uses or treatment regimens that are not included in the product's approved labeling (or, in the case of a medical device cleared under the 510(k) process, in the product's statement of intended uses). These off-label uses or treatment regimens may be important and may even constitute a medically recognized standard of care. Accordingly, the public health may be advanced by healthcare professionals' receipt of medical journal articles and medical or scientific reference publications on unapproved new uses of approved or cleared medical products that are truthful and not misleading.").

[14] Draft Guidance at 6.

[15] 21 U.S.C. § 321(m), (k).

[16] 335 U.S. 345, 348 (1948).

[17] *Id.* at 348, 350 (emphasis added).

[18] United States v. An Undetermined Number of Cases . . . "Sterling Vinegar and Honey . . . ," 338 F.2d 157, 158-59 (2d Cir. 1964).

[19] FDA has acknowledged that the list of items included in the regulation that is often cited as a definition of "labeling," 21 C.F.R. § 202.1(l)(2), simply operates to exclude certain forms of manufacturer communication from

communications such as reprints (whether "on-label" or "off-label"), CPGs, reference texts, or anything else that does not (among other criteria) function as an essential supplement to the label for the product.[20] The case for characterizing reference texts as labeling is particularly tenuous. Reference texts, commonly used by physicians in their practices, are obviously not designed for use in the sale of a drug or device, and an off-label discussion of a drug or device in a five-hundred-page textbook can hardly be considered an "essential supplement" to the product labeling. We believe that FDA's expansionist view of the term "labeling" oversteps the statutory authority and must be reconsidered.

B. Constitutional Limits on FDA's Authority

Members of the MIWG have described in previous regulatory submissions the constitutional boundaries that limit FDA's jurisdiction to regulate manufacturer speech.[21] Our 2013 citizen petition, in particular, described the implications of three recent court cases: *Sorrell v. IMS Health, Inc.*,[22] *FCC v. Fox Television Stations* (*Fox II*),[23] and *United States v. Caronia*.[24] These pivotal judicial decisions, together with prior decisions, establish the following principles:

First, content- and speaker-based restrictions on speech are "presumptively invalid."[25] The Supreme Court held in *Sorrell* that a regulatory scheme that "disfavors marketing"—*i.e.*, "speech with a particular content" and "specific speakers, namely pharmaceutical manufacturers" is content- and speaker-based; such regimes are subject to heightened scrutiny.[26]

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the scope of the advertising provisions of the FDCA and FDA regulations. Def.'s Summ. J. Reply at 22-23, *Allergan v. United States*, No. 09-1879 (D.D.C. filed Mar. 29, 2010). The only applicable legal definition of labeling therefore arises out of the statutory text itself (21 U.S.C. § 321(m)), a general regulatory definition of labeling in 21 C.F.R. Part 1 (§ 1.3(a)), and relevant case law.

[20] *See also* Citizen Petition, Docket No. FDA-2013-P-1079 (Sep. 3, 2013), at 13-14.

[21] The MIWG or its members have made nine 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); Citizen Petition, Docket No. FDA-2013-P-1079 (Sep. 3, 2013); MIWG, Comments re: Request for Comments Regarding FDA Safety and Innovation Act Section 907 Report, Docket No. FDA-2013-N-0745 (Nov. 20, 2013); MIWG, Comments re: Draft Guidance for Industry: Fulfilling Regulatory Requirements for Postmarketing Submissions of Interactive Promotional Media for Prescription Human and Animal Drugs and Biologics (Apr. 14, 2014) (Docket No. FDA-2013-N-1430). 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).

[22] *Sorrell v. IMS Health, Inc.*, 131 S. Ct. 2653 (2011).

[23] *FCC v. Fox Television Stations*, 132 S. Ct. 2307 (2012).

[24] *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012).

[25] *See Caronia*, 703 F.3d at 165 ("[T]he '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. Under the heightened scrutiny standard, restrictions on speech must be "narrowly drawn" to serve a "substantial" government interest. *Caronia*, 703 F.3d at 164. That is, the restriction must be both narrowly tailored and justified.

[26] *Sorrell* at 2664, 2667.

Second, less speech-restrictive methods, such as disclosure requirements, are favored over categorical bans on speech.[27] First Amendment jurisprudence disapproves of speech bans because they often arise from a "paternalistic assumption" that the listener will be unable to understand or utilize the information in an appropriate manner. Outright prohibitions on speech are especially problematic where, as here, the underlying conduct (*i.e.*, off-label use of drugs and devices) is entirely lawful.

Third, restrictions on speech must be sufficiently clear to give notice to regulated parties of what is prohibited.[28] Vagueness is "particularly treacherous" where the threat of criminal penalties "may deter those who seek to exercise protected First Amendment rights."[29]

We note that the *Draft Guidance* contains no substantive discussion of the First Amendment or other constitutional protections attendant to manufacturer speech, and we request that FDA reconsider the recommendations in light of these constitutional considerations and recent case law. The *Draft Guidance* at its core purports to distinguish between permissible and impermissible speech on the basis of content- and speaker-based restrictions, in direct contravention of the First Amendment principles espoused in *Sorrell* and *Caronia*.[30] For example, in addition to the fundamental distinction between on- and off-label content, the *Draft Guidance* favors content that meets all of the stringent standards outlined therein.[31] The *Draft Guidance* also prohibits certain types of speech by drug and device manufacturers, while the exact same content by other parties (*e.g.*, independent authors of journal articles, reference texts, or CPGs) is unregulated.[32] Such distinctions are subject to heightened scrutiny and are unlikely to pass constitutional muster.[33]

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[27] *See, e.g., 44 Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 496-97 (1996). Where less restrictive methods exist to render such lawful speech truthful and non-misleading, such as disclosure regimes, the First Amendment favors these methods over out-right bans on speech. *Zauderer v. Office of Disciplinary Counsel of the Sup. Ct. of Ohio*, 471 U.S. 626, 651 n. 14 (1985) ("[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."); *Caronia*, 703 F.3d at 168 (suggesting, as an alternative to a ban on promotion of new uses, development of "warning or disclaimer systems").

[28] The First and Fifth Amendments require clarity and precision in regulations that restrict speech. *See Reno v. ACLU*, 521 U.S. 844, 874 (1997)). Specifically, 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)). This requirement of clarity is particularly stringent in the area of speech. *Keyishian v. Bd. of Regents of the U. of N.Y.*, 385 U.S. 589,604 (1967); *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"). Harsh penalties, such as those faced by drug and device manufacturers found to engage in off-label promotion, magnify the need for precision because regulated entities will inevitably err on the side of less communication in order to avoid criminal sanctions.

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

[30] *Sorrell*, 131 S. Ct. at 2663; *Caronia*, 703 F.3d at 164.

[31] For example, content that is based on adequate and well-controlled studies, free from manufacturer influence, and subjected to other robust criteria (*e.g.*, peer review, a "systematic review of the evidence" for reference texts and clinical practice guidelines). *See, e.g.,* Draft Guidance at 7, 11, 14.

[32] The FDCA authorizes FDA to regulate some forms of manufacturer speech, but it is the resulting burden—as opposed to statutory authority—that is ultimately relevant to the determination of whether a particular restriction on speech is constitutional. *See, e.g.*, Sorrell at 2663.

[33] *Id.*

The *Draft Guidance* also proposes to restrict certain forms of manufacturer communication rather than recommending that such communications be accompanied by robust disclosures. By significantly limiting the scope of materials that may be disseminated under the *Draft Guidance*, FDA assumes that health care professionals do not have the capacity or professional judgment necessary to evaluate the quality of information received from manufacturers. Discouraging the flow of truthful, non-misleading information on the basis that physicians may misinterpret its weight or apply it incorrectly is inconsistent with the First Amendment when less restrictive means such as disclaimers are available.[34]

Finally, many of the recommendations in the *Draft Guidance* incorporate undefined terms or are otherwise vague. The *Fox II* decision emphasizes that the government must set forth clear and precise boundaries in the area of speech regulation before taking enforcement action,[35] yet a lack of compliance with the *Draft Guidance* could be used by FDA as evidence of a new intended use.[36] Without clearer distinctions between permitted and prohibited activity, manufacturers will have significant difficulties attempting to comply with the recommendations in the *Draft Guidance*, and due to the threat of enforcement, may be less likely to disseminate truthful, non-misleading off-label information that benefits the public health.

III. Comments on Specific Aspects of the *Draft Guidance*

In addition to the core concerns described above, we offer a number of comments applicable to particular aspects of the *Draft Guidance*.[37] At the outset, we broadly note that the recommendations and examples provided in the *Draft Guidance* reflect a traditional view of company interactions with health care professionals that was common at the time FDA's advertising regulations were promulgated; such interactions are now frequently occurring through electronic channels such as e-mail, video conferencing, and other closed-access meeting platforms, and we ask FDA to be mindful of these new communication technologies as it finalizes the *Draft Guidance*. We also ask that FDA consider the following recommendations so as to better align the *Draft Guidance* with constitutional principles, to enhance clarity, and to increase compliance among manufacturers.

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[34] *See 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."); *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.").

[35] *Fox II*, 132 S. Ct. at 2318.

[36] Draft Guidance at 6.

[37] Note that the concerns described herein are not exhaustive; we have limited our specific comments to those that are most fundamental to the MIWG's efforts in seeking FDA alignment with constitutional and statutory limits on the regulation of speech.

A. Comments Applicable to Reprints, Reference Texts, and CPGs

1. *"False or Misleading" Standard*

The *Draft Guidance*'s description of the conditions under which information for journal articles, reference texts, or CPGs would be considered "false or misleading" is of great concern. Our rationale and proposals for amending the *Draft Guidance* are stated below.

a. Scientific or Medical Journal Articles

Under the *Draft Guidance*, a journal article would be "false or misleading" and thus ineligible for the safe harbor if "a significant number of other studies contradict the conclusions set forth in the article." The *Draft Guidance* also lists as an example of a "false or misleading" journal article one that "discuss[es] a clinical investigation that FDA has previously informed the company is not adequate and well-controlled." Evidence from such studies is not necessarily false or misleading, however. Even if a particular clinical investigation is contradicted by a number of other studies, the investigation itself or any report thereof is not false or misleading simply because it resulted in a different outcome. The *Draft Guidance* implicitly recognizes this by recommending that manufacturers include a representative publication that reaches a different or contrary outcome from the primary article. Moreover, if a journal article is "false or misleading" if a "significant number of other studies contradict the conclusions . . . in the article," a significant portion of the medical literature would be considered "false or misleading." Indeed, all iconoclastic journal articles would be false or misleading under such a standard. FDA's determination during the approval process or otherwise that a study does not meet the agency's approval standard similarly does not render the investigation false or misleading. That approach disregards the fact that data from a variety of sources can provide information highly relevant to the use of the drug, even if the investigation is not a prospective randomized controlled trial. So long as the medical or scientific journal article is truthful and non-misleading and clearly discloses the nature and design of the study, the study design itself should not be a factor in the false-or-misleading determination.

The MIWG therefore proposes that FDA modify the "false or misleading" standard for journal articles to state: "A scientific or medical journal article that explains a use of a manufacturer's product and is distributed by, or on behalf of, that manufacturer must not: 1. Be false or misleading. For example, *a manufacturer should disclose whether* a distributed journal article ~~should not be characterized as definitive or representative of the weight of credible evidence derived from adequate and well-controlled clinical investigations if it~~ is inconsistent with the weight of credible evidence, if a significant number of other studies contradict the conclusions set forth in the article, or has ~~should not have~~ been withdrawn by the journal or disclaimed by the author~~; or and should not discuss a clinical investigation that FDA has previously informed the company is not adequate and well-controlled~~."

b. Reference Texts and Clinical Practice Guidelines

The prohibition against false or misleading reference texts and CPGs is unnecessary and should be eliminated. The *Draft Guidance* contains numerous other recommendations designed to ensure that materials disseminated are truthful and non-misleading. Reference texts

distributed under the *Draft Guidance*, for example, will be peer-reviewed, authored by experts in the field, and presented without markings or other characterizations made by the manufacturer.[38] CPGs will be shared only if developed by a multidisciplinary panel of experts and revised as needed to account for new evidence.[39] Provided that these and other recommendations are followed by the manufacturer disseminating the material, there is no reason to engage in an independent analysis of whether the material may be false and misleading.

Additionally, we are aware of no publishers or organizations that meet FDA's requirements for independence yet produce false and misleading textbooks or CPGs. Furthermore, FDA has offered no guidance to manufacturers regarding how to determine if reference texts or CPGs are false or misleading in the agency's view. Requiring manufacturers to comb through these materials in their entirety in an attempt to ascertain whether FDA would consider them false or misleading in any respect raises serious constitutional issues, as does the agency's position that dissemination of such materials should be prohibited altogether if any aspect of them is found to be false or misleading.[40] We therefore urge FDA to strike this recommendation for reference texts and CPGs.

2. *Ban on Publications Edited or Significantly Influenced by Individuals Having a Financial Relationship with the Manufacturer*

The *Draft Guidance* recommends that manufacturers should not disseminate publications that were "edited or significantly influenced by a drug or device manufacturer or any individuals having a financial relationship with the manufacturer."[41] The MIWG opposes the inclusion of such rigid limitations on the dissemination of scientific and medical publications.[42] Such a ban is overbroad, lacks clarity, and may effectively prevent the distribution of these materials altogether, to the detriment of public health and in contravention of the First and Fifth Amendments.

This prohibition would severely limit the ability of a manufacturer to circulate scientific or medical publications, because many such publications are in fact authored or influenced by individuals having a financial relationship with the manufacturer. Indeed, FDA itself has previously acknowledged that there are useful articles written or published by manufacturers.[43] Authors of articles describing clinical studies, for example—including pivotal, on-label studies—by definition have financial ties because manufacturers pay them to conduct the research. It is also routine for company employees (*e.g.*, medical affairs or research personnel) to serve as co-authors of articles describing clinical investigations, whether those investigations relate to on- or

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[38] Draft Guidance at 11-13.
[39] *Id.* at 14-17.
[40] *See supra* notes 28, 27.
[41] *Id.* at 9, 13, 17.
[42] We would also remind FDA that, in the context of the agency's regulation of industry-supported scientific and educational activities, district and appellate federal courts previously suggested that an outright ban on the dissemination of off-label information was unconstitutional because it was not the least restrictive means of advancing the government interest. Although the injunctions and court decisions limiting FDA's policies were subsequently vacated due to intervening events, the constitutional implications of agency restrictions on manufacturer speech persist. *See Washington Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 74 (D.D.C. 1998) ("*WLF I*"), *vacated in part & app. dismissed on other grounds sub nom. Washington Legal Found. v. Henney*, 202 F.3d 331 (D.C. Cir. 2000) ("*WLF II*").
[43] 61 Fed. Reg. 52,800, 52,801 (Oct. 8, 1996).

off-label uses. All of these individuals may be involved in the design of the underlying study, may have highly specialized knowledge with respect to the drug or device at issue, and may make invaluable contributions to the analysis of the data or development of the manuscript.

This prohibition is especially problematic as applied to reference texts, which may include contributions from dozens or even hundreds of experts. Not only would it be burdensome to expect manufacturers to examine the financial relationships of every contributor of each text prior to dissemination, but it would significantly limit the reference texts that could be disseminated under the *Draft Guidance*, because the experts asked to contribute to texts are often the same individuals asked to advise drug and device manufacturers on issues relating to research and product development. The fact that a scientific or medical publication has been edited or influenced by individuals with a financial relationship with the manufacturer does not undermine the quality of the information. Restricting the dissemination of these publications—preemptively and without regard to content—simply because such individuals have edited or significantly influenced them would ignore the realities of how scientific and medical publications are developed and would result in most publications being excluded from the *Draft Guidance*.

The recommendation additionally conflicts with First and Fifth Amendment principles. Distinguishing between permissible and impermissible speech on the basis of the manufacturer's influence or the identity of the author represents an inappropriate speaker-based restriction under the First Amendment. The approach also constitutes a categorical ban on speech where a less restrictive mechanism—namely, requiring disclosure of any influence or interest—is available to serve the same ends. Many journal publishers, in fact, require robust disclosure of "financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing" articles submitted for publication."[44] The *Draft Guidance* itself already provides for such a disclosure regime for articles with authors having financial relationships with manufacturers, thereby implicitly acknowledging that such relationships (and correspondingly, the influence that arguably attaches to them) do not inherently undermine the value of the published information. Disclosure of financial relationships between authors and manufacturers—as opposed to an outright ban on articles, reference texts, or CPGs authored by those individuals—would be more consistent with the First Amendment. Additionally, the *Draft Guidance* poses Fifth Amendment concerns because it does not define what it means for a manufacturer to "significantly influence" a publication.[45] Manufacturers will not know how to comply with this vague recommendation and may censor themselves from engaging in protected speech as a result.

In order to effectuate the purposes of the disclosure regime, comport with constitutional principles, and allow the distribution of publications beneficial to the public health, the MIWG recommends that the language excluding manufacturer-influenced publications from the safe harbor be struck from the *Draft Guidance*. The MIWG further proposes that the final guidance supplement the disclosure requirements by adding the following required disclosure: "*Any influence of the manufacturer on the publication, including whether the publication was written,*

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[44] *See, e.g.*, International Committee of Medical Journal Editors, Form for Disclosure of Potential Conflicts of Interest, *available at* http://www.icmje.org/downloads/coi_disclosure.pdf.
[45] *See supra* note 28.

edited, excerpted, or published specifically for, or at the request of, the manufacturer, or was edited or significantly influenced by the manufacturer or any individuals employed by or who otherwise have a financial relationship with the manufacturer."

3. *Disclosure of the "Nature and Amount" of Financial Interest Received by an Author from a Manufacturer*

For article reprints and individual sections or chapters of reference texts or CPGs, the *Draft Guidance* recommends that the manufacturer affix a sticker to the material identifying any author having a "financial interest" in the manufacturer or one of its products, as well as "the nature and amount of any such financial interest of the author or compensation received by the author from the manufacturer." Because the *Draft Guidance* does not define "financial interest," it is unclear what type of relationship would qualify (*e.g.*, research grants, consulting arrangements, stock ownership, employee compensation). Without clear instructions to manufacturers on how to implement this recommendation, they will not know how to comply. There are also significant privacy concerns associated with this recommendation, as it would result in a manufacturer publicly revealing financial information—including, for example, the compensation received by one of its own employees or ownership of publicly traded equity—on every scientific or medical publication disseminated. Additionally, we note that the Open Payments Law, or Physician Payments Sunshine Act, already requires disclosure of any financial relationships of manufacturers and health care professionals, creating the transparency needed to assess potential conflicts of interest without the privacy implications associated with divulging sensitive matters such as employee compensation, or the compliance burdens associated with interpreting a vague recommendation, continually reevaluating financial relationships, and updating the required disclosures as the nature and amount of financial interests evolve. Finally, we are aware of no evidence to suggest that providing the *amount* of the financial interest is required to avoid misleading the health care professional receiving the material; indeed, journal publishers themselves have determined that disclosing the general nature of the financial interest is sufficient to address potential conflicts of interest.[46] We therefore request that FDA more clearly explain what it means by an author's "financial interest" and revise the recommendation as follows: "The disclosure must explicitly name any author known to the manufacturer as having a financial interest in the manufacturer or in a product of the manufacturer that is included in the [journal article, reference text chapter, or CPG section], or who is receiving compensation from the manufacturer, along with the affiliation of the author, to the extent known by the manufacturer~~, and the nature and amount of any such financial interest of the author or compensation received by the author from the manufacturer~~."

4. *Disclosure of "All Significant Risks or Safety Concerns Associated with the Unapproved Uses of the Manufacturer's Products Discussed in the [Publication]"*

The *Draft Guidance* retains the requirement that all scientific and medical publications be distributed with disclosure of "all significant risks or safety concerns associated with the

[46] *See, e.g.*, International Committee of Medical Journal Editors, Form for Disclosure of Potential Conflicts of Interest, *available at* http://www.icmje.org/downloads/coi_disclosure.pdf.

unapproved uses of the manufacturer's products discussed in the scientific or medical publication that are known to the manufacturer but not discussed in the scientific or medical publication."

This disclosure requirement is vague, and manufacturers will not know how to comply. Specifically, without any guidance on what constitutes a "significant" risk or safety concern, it is unclear what risks manufacturers are required to disclose. In addition, it is unclear what form such disclosure must take (*e.g.*, distribution of entire publications disclosing risks, excerpts explaining risks, list of risks), and what information about each risk must be disclosed. The MIWG therefore recommends that the FDA clarify (1) what risks reach the level of "significant;" (2) what form disclosures of such risks must take; and (3) what information must be disclosed about each risk.

5. *Characterization of Information that is "Promotional in Nature"*

The *Draft Guidance* recommends that all medical or scientific publications referencing off-label uses be distributed "separately from the delivery of information that is promotional in nature."[47] Among the examples provided to clarify this recommendation, FDA states that "while a [publication] may be distributed at medical or scientific conferences in settings appropriate for scientific exchange, the [publication] should not be distributed in promotional exhibit halls or during promotional speakers' programs."[48] FDA has offered no evidence that simply disseminating reprints—whether in a commercial booth or other setting—will result in conversations about the off-label content, especially considering that companies' robust compliance programs are designed to discourage and root out such behavior. We contend that dissemination of scientific and medical publications would be appropriate in commercial booths. After all, the *Draft Guidance* explicitly contemplates that a sales representative may disseminate a scientific or medical publication during a visit to a physician's office; allowing one practice but not the other is arbitrary. We therefore request that FDA delete the example relating to commercial booths.

B. The Recommendation that Reprints of Journal Articles Report Adequate and Well-Controlled Clinical Investigations

The *Draft Guidance* generally recommends that reprints of scientific or medical journal articles distributed by manufacturers should address "adequate and well-controlled clinical investigations that are considered scientifically sound by experts with scientific training and experience to evaluate the safety or effectiveness of the drug or device."[49] While this recommendation is largely consistent with that of the 2009 *Reprints Guidance*, the *Draft Guidance* no longer provides, as the 2009 *Reprints Guidance*[50] did, that information contained in a scientific or medical journal article "can include historically controlled studies, pharmacokinetic (PK) and pharmacodynamic (PD) studies, and meta-analyses if they are testing a clinical hypothesis." The *Draft Guidance* instead states that, "[i]n the case of devices, significant investigations other than adequate and well-controlled studies, such as meta-analyses, if they are testing a specific clinical hypothesis, and journal articles discussing significant non-

[47] Draft Guidance at 8, 11, 15.
[48] *Id.*
[49] *Id.* at 7.
[50] *See* 2009 Reprints Guidance at 4.

clinical research (such as well-designed bench or animal studies) may be consistent with this guidance."[51] As currently written, the *Draft Guidance* implies by omission that drug manufacturers may not distribute reprints discussing meta-analyses, PK or PD studies and other significant non-clinical research.

FDA's approach unnecessarily deprives health care practitioners of accurate, up-to-date, clinically relevant information. We acknowledge that, under the FDCA, new drug manufacturers must provide to FDA through the premarket review process "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof."[52] The statute defines "substantial evidence" to mean "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved,"[53] and FDA by regulation has described the characteristics a study must have to qualify as "adequate and well-controlled" and thus support claims of a particular drug's effectiveness for purposes of market approval.[54] The agency has also applied the substantial evidence standard in the promotional context.[55] However, applying premarket review and promotional standards to non-promotional content disseminated under the *Draft Guidance* is unnecessary and inappropriate.

Even if a clinical investigation does not meet FDA's approval standard for a new use, it still may provide meaningful information regarding the use of a drug. Indeed, FDA itself has recognized that data from a variety of sources, including meta-analyses, open-label studies, and "other valid scientific evidence" may be clinically valuable with respect to drugs as well as devices.[56] Severely limiting the circumstances under which a manufacturer may disseminate truthful and non-misleading off-label use information—especially in light of the other recommendations, such as the need for peer review—undermines the notion that health care professionals are trained and equipped to evaluate the weight of different types of evidence. A clinician may well understand that an adequate and well-controlled study represents the "gold standard" of safety and effectiveness data, but in many cases such data are not available; moreover, when treating ultra-rare conditions, or working in fields like oncology where clinical practices are rapidly evolving, an up-to-date case series or retrospective subgroup analysis may ultimately prove to be more valuable in the treatment of a particular patient.

These limitations also conflict with First Amendment values by restricting the dissemination of truthful, non-misleading, scientifically substantiated information to health care

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[51] *See* Draft Guidance at 7-8.
[52] 21 U.S.C. § 355(d).
[53] *Id.*
[54] FDA considers "adequate and well-controlled" studies to have the following features: (1) a protocol containing a clear statement of the study's objectives and methods of analysis; (2) a design that permits a valid comparison with a control, (3) a method of selecting subjects that assures they actually have the disease being studied; (4) a method of assigning subjects to treatment and control groups that minimizes bias and is intended to assure comparability of the groups with respect to pertinent variables, such as severity of disease, duration of disease, and use of other therapies; (5) adequate measures to minimize bias, such as blinding; (6) well-defined and reliable methods for assessing subject response; and (7) analysis of results that is adequate to assess the effects of the drug. 21 C.F.R. § 314.126.
[55] *See, e.g.*, 21 C.F.R. § 202.1.
[56] 63 Fed. Reg. 64,556, 64,559 (Nov. 20, 1998).

practitioners. As described in Part II.B., above, the safe harbor as currently proposed by FDA is content-based. The agency is effectively prohibiting distribution of journal articles that describe a broad range of studies and provide other meaningful product information on the ground that the articles do not comport with FDA's own narrow view of which information is scientifically reliable. To escape the threat of enforcement, manufacturers must generally limit themselves to distributing adequate and well-controlled studies—even when more recent, high-quality data may be available from other sources. Health care professionals and payers are thereby limited in the information they may receive under the *Draft Guidance*, in contravention of the First Amendment.[57] 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.[58] Disclosure systems are preferred because they "open the channels of communication, rather than . . . close them," enabling informed individual choice.[59] Permitting distribution of a broader range of materials, but requiring manufacturers to disclose any relevant limitations of the underlying study data, would be both consistent with the First Amendment and achieve the public health goal of communicating truthful, non-misleading off-label use information to health care professionals.

FDA's decision in the *Draft Guidance* to narrow its interpretation of adequate and well-controlled studies applicable to drug manufacturers so as to eliminate historically controlled studies, meta-analyses, PK, or PD studies is similarly ill-conceived. We are aware of nothing to suggest that FDA's policy from the 2009 *Reprints Guidance*, which permitted both drug and device manufacturers to disseminate such studies, was unworkable or resulted in a threat to the public health. To the contrary, such studies may be invaluable to patient care; meta-analyses, for example, may involve significantly more patients than controlled clinical trials, and historically controlled studies may provide important information about how patients respond to a treatment in real-world conditions. FDA has itself repeatedly recognized the value of studies that are not adequate-and-well controlled, determining that they may constitute "substantial evidence" and form the basis for market approval in some circumstances.[60] Further limiting the circumstances under which drug manufacturers may share off-label use information implicates serious constitutional questions, especially given that the *Draft Guidance* creates an artificial distinction based solely on the identity of the speaker—an approach deemed presumptively invalid in *Sorrell*.[61] Moreover, the parameters governing which articles device manufacturers may appropriately distribute under the *Draft Guidance* are poorly defined. While the *Draft Guidance* allows device manufacturers to share results of "significant" investigations that are not adequate and well-controlled, or "significant" non-clinical research, FDA has offered no guidance to help manufacturers determine the significance of a particular investigation. Similarly, the *Draft Guidance* refers to "well-designed" bench or animal studies that may be disseminated by device manufacturers but does not further define that term. A lack of precision in these terms may lead

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[57] *See, e.g., Sorrell* at 2664 (noting that the speaker and the audience, as opposed to the government, have the right to assess the value of information).

[58] *Caronia*, 703 F.3d at 168 (suggesting, as an alternative to a ban on promotion of new uses, development of "warning or disclaimer systems"); *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)).

[59] *See* Va. Bd. of Pharmacy, 425 U.S. at 770.

[60] See C. Klasmeier and T. Cope, *NDA Approval Under FDCA Section 505(b)(1) Based on Effectiveness Data from One Clinical Trial* (Jan. 2012).

[61] *Sorrell* at 2660-63.

manufacturers to limit the dissemination of article reprints even though they contain clinically relevant information; the chilling effect of this uncertainty undermines the value of the safe harbor and directly implicates the First Amendment.[62]

Allowing dissemination of truthful and non-misleading journal articles about a clinical study, whether or not it is deemed an acceptable study by the agency for purposes of marketing authorization, would recognize that clinically meaningful information may emerge from a variety of sources and would better comport with the First Amendment. We therefore request that FDA revise the *Draft Guidance* to make clear that journal articles disseminated by manufacturers need not concern a clinical investigation that meets the "adequate and well-controlled" standard, so long as the articles are truthful and non-misleading and the study design and limitations are described in the publication or accompanying manufacturer disclosure. If FDA is unwilling to delete the reference to adequate and well-controlled investigations, we request at a minimum that the agency permit both drug and device manufacturers to distribute reprints discussing historically controlled studies, meta-analyses, PK or PD studies, and other significant non-clinical research.

C. The Recommendation that Reference Texts and CPGs be Based on a "Systematic Review of the Evidence"

The *Draft Guidance* recommends that reference texts and CPGs disseminated by manufacturers be based on a "systematic review of the existing evidence."[63] The phrase is not defined in the *Draft Guidance* and to our knowledge has no basis in previous statements of FDA policy relating to reference texts. This lack of precision raises serious First and Fifth Amendment concerns, particularly because manufacturers that fail to apply the standard may not qualify for the safe harbor and may therefore risk government enforcement for "promoting" a new intended use. It is also unclear from the *Draft Guidance* who is responsible for making the determination that a particular text or CPG is indeed based on a systematic review of the evidence. To the extent that FDA expects manufacturers to perform this task, the MIWG submits that this requirement will be burdensome and infeasible to implement, especially with respect to reference texts. Most manufacturers have promotional review committees ("PRCs") charged with reviewing promotional and other materials (*e.g.*, reprints of scientific journal articles) to ensure compliance with FDA promotional rules, but those responsibilities apply in most cases to a single product, or set of products; indeed, these committee members are frequently selected for their specialized knowledge with respect to a particular product, or at a minimum, receive extensive training about the products referenced in the materials they are tasked with reviewing. Because reference texts often discuss a variety of diseases and conditions and mention dozens of therapies, clinical trials, and relevant considerations for treating patients, PRC members may not be qualified to assess whether a reference text is based on a systematic review of the evidence. Analyzing a reference text in detail to make this determination also promises to be so time- and resource-intensive that many manufacturers would be unwilling to engage in the exercise and would choose instead to avoid dissemination of the material altogether. Finally, because the *Draft Guidance* also contains recommendations for reference texts and CPGs that go directly to the quality of the data and analysis contained within them, the

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[62] *See, e.g., id., see also Caronia*, 703 F.3d at 165.
[63] Draft Guidance at 11, 14.

systematic-review determination is unnecessarily duplicative and would result in manufacturers second-guessing the work of the individuals involved in the textbook and CPG development and publication process. We therefore urge FDA to strike this recommendation.

D. The Trustworthiness Criteria for CPGs

The MIWG appreciates that FDA has added CPGs to the materials that may be disseminated pursuant to the *Draft Guidance*. As described in detail in two citizen petitions submitted by MIWG members, CPGs developed by leading associations of medical professionals, academic institutions, and government agencies are invaluable to the proper diagnosis, disease management, and treatment of patients.[64] We assert, however, that the information contained in a CPG may be high-quality, up-to-date, and clinically meaningful even if it does not fully comport with the IOM's criteria for trustworthiness. A recent article in the *Journal of Clinical Oncology*, for example, reviewed 169 CPGs relating to the four leading causes of cancer mortality in the United States and determined that not a single one met the IOM standard for trustworthiness.[65] The authors nevertheless concluded that "many quality guidelines do exist," demonstrating that CPGs may be clinically relevant and deemed credible by experts in the field even when they do not satisfy the IOM criteria."[66] While we are mindful of FDA's interest in the external validation of CPGs, we are concerned that the agency's rigid application of the IOM trustworthiness criteria would be unworkable in practice and would ultimately deprive health care professionals of important information. We therefore urge FDA to develop more flexible criteria for the dissemination of CPGs.

E. Other Recommendations Relating to Reference Texts

The *Draft Guidance* recommends that, when an individual reference text chapter devotes "primary substantive discussion" to a manufacturer's product, the manufacturer should include the approved product labeling when disseminating the text. It also recommends that manufacturers disseminate not only the individual chapter containing a product discussion, but also any other chapters "when necessary to provide context."[67] Neither of these terms is defined in the *Draft Guidance*, and as a result, the recommendations are impermissibly vague.[68] Without an explanation of when chapters contain a "primary substantive discussion" or are "necessary to provide context," manufacturers will not know how to comply with these requirements. There is accordingly a risk that, in order to avoid liability, manufacturers will simply refrain from distributing reference texts or relevant excerpts as envisioned in the *Draft Guidance*. The

[64] Citizen Petition, Docket No. FDA-2013-P-1079 (Sept. 3, 2013), at 10-11; Citizen Petition, Docket No. FDA-2011-P-0512 (July 5, 2011), at 11-12.
[65] Reames et al., *Clinical Evaluation of Oncology Clinical Practice Guidelines*, 31 J. of Clin. Oncology 2563, 2563-65 (2013).
[66] *Id.* at 2567.
[67] Draft Guidance at 12, 16.
[68] *See Reno*, 521 U.S. at 874; *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").

resulting self-censorship burdens a broad array of protected speech under the First Amendment and deprives health care practitioners of clinically meaningful information.

We appreciate the opportunity to comment on the *Draft Guidance*. We look forward to the resolution of the issues we have identified.

Respectfully submitted,

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