SIDLEY AUSTIN LLP
SIDLEY

ROPES
&GRAY

August 25, 2014

Via Electronic Submission

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Draft Guidance for Industry: "Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products—Recommended Practices" (Docket No. FDA–2014–D–0758)

The Medical Information Working Group ("MIWG")[1] welcomes the opportunity to provide the Food and Drug Administration ("FDA") with comments on the draft guidance "Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products—Recommended Practices" ("*Draft Guidance*"), pursuant to the Federal Register notice dated June 11, 2014.

As described in our previous submissions,[2] the MIWG has long been committed to protecting and promoting the public health by working toward a regulatory and enforcement climate that enables payers, prescribers, patients, and other stakeholders to make informed health

[1] The MIWG is a coalition of medical product manufacturers formed to consider issues relating to the federal government's regulation of truthful, non-misleading, scientifically substantiated manufacturer communications about new uses of approved drugs and approved/cleared medical devices. The members of the MIWG are: 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[2] The MIWG and its members have made these submissions to the Agency since 2008: (1) Comments, Draft Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices, Docket No. FDA-2008-D-0053 (Apr. 18, 2008); (2) Amended Comments, FDA Transparency Task Force, Docket No. FDA-2009-N-0247 (Apr. 15, 2010); (3) Citizen Petition, Docket No. FDA-2011-P-0512 (July 5, 2011); (4) Comments re: Scientific Exchange and Responses to Unsolicited Requests, Docket Nos. FDA-2011-N-0912 and FDA-2011-D-0868 (Mar. 27, 2012); (5) Comments, Docket Nos. FDA-2011-P-0512 and FDA-2011-D-0868 (Mar. 1, 2013); (6) Comments, CDER Medical Policy Council, Docket No. FDA-2013-N-0206 (July 16, 2013); (7) Citizen Petition, Docket No. FDA-2013-P-1079 (Sept. 3, 2013); (8) Comments, Food and Drug Administration Safety and Innovation Act Section 907 Report (Nov. 20, 2013); (9) Comments, Draft Guidance for Industry: Fulfilling Regulatory Requirements for Postmarketing Submissions of Interactive Promotional Media for Prescription Human and Animal Drugs and Biologics, Docket No. FDA-2013-N-1430 (Apr. 14, 2014); (10) Comments, Draft Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses- Recommended Practices, Docket No. FDA-2008-D-0053 (May 2, 2014); and (11) Comments re: FDA's Draft Strategic Priorities for 2014–2018, Docket No. FDA-2014-N-0833 (Jul. 31, 2014). 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*, No. 09-5006-CR, 703 F.3d 149 (2d Cir. 2012).

care decisions. Information that refines, updates, or augments the product labeling is central to such decision-making, and we appreciate that the *Draft Guidance* explicitly permits manufacturers to share such information in certain circumstances. More broadly, we are pleased that FDA recently responded to our citizen petitions by agreeing to engage in a comprehensive review of the regulatory scheme governing manufacturer speech in an effort to harmonize it with the First Amendment.[3] Fundamentally, though, we are concerned that despite this ongoing review, FDA continues to regulate manufacturer speech by delineating narrow safe harbors in non-binding guidance documents, without setting forth unifying principles to guide the sharing of truthful, non-misleading product information. The Agency's incremental approach engenders confusion, results in categorical distinctions not sufficiently grounded in the law or the protection of the public health, and deters manufacturers from communicating information that is in fact protected by the First Amendment.

The *Draft Guidance* exemplifies the concerns with FDA's piecemeal approach. While the *Draft Guidance* rightfully facilitates informed decision-making by permitting manufacturers to share emerging risk information that is related, but not identical, to the product labeling, and by allowing company representatives to discuss that information with the recipient, it is unduly narrow in certain respects and does not articulate a clear and constitutionally sufficient basis for permitting certain types of manufacturer speech while prohibiting others. In Part I of these comments, we describe the constitutional framework that limits FDA's ability to restrict truthful, non-misleading speech, and we describe the ways in which the *Draft Guidance* is inconsistent with those limiting principles. Part II addresses the *Draft Guidance*'s distinction between emerging risk information and emerging effectiveness information and underscores their collective value to the public health. In Part III, we discuss specific recommendations in the *Draft Guidance* that do not clearly define the boundaries between permissible and impermissible conduct as required by the Constitution.

I. The Constitutional Framework Applicable to the *Draft Guidance*

Medical product communications and speech regarding scientific research are highly valuable and are protected by the First Amendment. The free flow of speech "has great relevance in the fields of medicine and public health, where information can save lives."[4] In recent years, courts have made it increasingly clear that FDA's regulatory authority over the sale of medical products does not permit it to broadly prohibit truthful, non-misleading communications regarding such products.[5] This is not least because payers, physicians, and patients, too, have a constitutionally protected interest in the free flow of information from a range of sources.[6] Accordingly, the Supreme Court has expressly declared that "[s]peech in aid of pharmaceutical marketing," in particular, "is a form of expression protected by the Free

[3] *See, e.g.*, Letter from Leslie Kux, Assistant Commissioner for Policy, to Alan R. Bennett, Joan McPhee, Coleen Klasmeier, and Paul E. Kalb, Docket Nos. FDA-2011-P-0512 and FDA-2013-P-1079, 9 (June 6, 2014).
[4] *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653 (2011).
[5] *See, e.g.*, *Thompson v. W. States Med. Ctr.*, 535 U.S. 357 (2002).
[6] *See Sorrell*, 131 S. Ct. at 2671-72; *see also Virginia State Bd. of Pharm. v. Virginia Citizens Consumer Council, Inc.*, 425 U.S. 748, 756-57 (1976).

Speech Clause of the First Amendment," and content- and speaker-based regulation of this expression "must be subjected to heightened judicial scrutiny."[7]

Notably, the First Amendment disfavors categorical bans on speech because they evidence a "paternalistic assumption" that the government—as opposed to the speaker or listener—is best-equipped to assess the meaning and value of the information.[8] The government therefore may not prohibit speech on the ground that it may be misleading when potential concern for confusion on the part of the audience can be ameliorated by adequate disclosures regarding the quality of the evidence underlying the speech.[9] The First Amendment protects a speaker's right to disseminate information from different sources of evidence, including evidence that may be subject to legitimate and ongoing scientific debate.[10]

While the First Amendment limits the reach of FDA's regulation of manufacturer speech, the Constitution similarly requires that the restrictions be clear and sufficiently well-defined to guide manufacturers' conduct. The Due Process Clause of the Fifth Amendment assigns agencies the burden to provide "fair notice of what is prohibited,"[11] and this burden applies with particular force in the area of speech regulation.[12] Vagueness in FDA's speech restrictions is problematic because it chills manufacturers from communicating information that is both highly valuable and protected by the First Amendment.[13] The chilling effect is especially pronounced when the threat of criminal sanctions is present; in such circumstances, regulated parties who are unable to distinguish between permissible and impermissible conduct will inevitably err on the side of less communication to avoid criminal penalties and other sanctions.[14]

Although FDA has previously recognized that product labeling is not the most comprehensive and up-to-date resource for clinically relevant information,[15] the Agency has long insisted that the substantial evidence standard serves to restrict manufacturers from joining in the scientific discourse about their products unless their statements are supported by two adequate and well-controlled studies. This discordance between accurate information and information that

---

[7] *Sorrell*, 131 S. Ct. at 2659.

[8] *See, e.g., United States v. Caputo*, 517 F.3d 935, 938–39 (7th Cir. 2008) ("[T]he Constitution forecloses an enforced ignorance based on a paternalistic view that informed consumers will make mistakes.").

[9] *See Ony, Inc. v. Cornerstone Therapeutics, Inc.*, 720 F.3d 490, 498 (2d Cir. 2013). Outright prohibitions on speech are especially problematic where, as here, the underlying conduct (*i.e.*, a clinician's decision to prescribe a drug on the basis of information not contained in the product labeling) is entirely lawful. *See, e.g., United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012).

[10] *See Ony*, 720 F.3d at 498.

[11] *FCC v. Fox Television Stations*, 132 S. Ct. 2307, 2318 (2012) ("*Fox II*").

[12] *See id.*; *see also Keyishian v. Bd. Of Regents of the U. of N.Y.*, 385 U.S. 589, 604 (1967) (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.").

[13] *Reno v. ACLU*, 521 U.S. 844, 871-72 (1997) (Vagueness in speech regulation "raises special First Amendment concerns because of its obvious chilling effect . . . .").

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

[15] *See e.g.*, 63 Fed. Reg. 64556, 64579 (Nov. 20, 1998) (recognizing the importance of early dissemination of objective, balanced, and accurate information that is not in the labeling); *see also* 40 Fed. Reg. 15392, 15394 (Apr. 7, 1975) ("[T]he labeling of a marketed drug does not always contain all the most current information available to physicians relating to the proper use of the drug in good medical practice. Advances in medical knowledge and practice inevitably precede labeling revision."); *see also* Robert Temple, *Legal Implications of the Package Insert*, 58 Med. Clinics of N. Am. 1151, 1155 (1974) (noting that labeling "cannot be both authoritative and avant garde.").

may be shared by manufacturers, as we have argued in prior submissions to FDA, has profound implications under the First Amendment and for the public health.[16]

We recognize that the *Draft Guidance* represents an important step forward in the regulatory scheme governing manufacturer communications. For the first time, FDA has in the *Draft Guidance* explicitly permitted manufacturers to communicate proactively with payers, prescribers, and other stakeholders about emerging risk information that is related to, but not set forth verbatim in, the approved product labeling; moreover, the *Draft Guidance* appropriately permits company representatives to discuss the information with recipients rather than simply provide a copy of the underlying study or analysis.[17] While we welcome these developments, they do not satisfy the Agency's burden to ensure that the entire *Draft Guidance*, as well as the broader regulatory scheme, be consistent with the constitutional principles described above.

Despite the Agency's stated recognition of the First Amendment case law and its commitment to engage in a comprehensive review of its regulations and policies governing manufacturer communications,[18] the *Draft Guidance* contains no reference to the Constitution and does not adequately reflect the First Amendment principles that have evolved over a number of years[19] and were crystallized in the *Sorrell* and *Caronia* decisions. The *Draft Guidance* is reminiscent of other guidance documents recently issued by FDA, all of which carve out exceedingly narrow circumstances under which manufacturers may communicate truthful and non-misleading information about their products without acknowledging that the First Amendment would permit broader communications;[20] indeed, the safe harbor created by the *Draft Guidance* is so limited that it applies only to emerging information that rebuts, refines, or mitigates information about known and labeled risks. As such, the safe harbor would not protect, for example, dissemination of information regarding entirely new risks or information indicating that a risk already identified in approved labeling is more serious than previously thought. The *Draft Guidance* also fails to correct the Agency's constitutionally deficient content- and speaker-based approach to regulating speech about medical products. Specifically, the *Draft Guidance* perpetuates a regulatory framework that prohibits certain forms of speech by drug manufacturers while allowing other parties (*e.g.*, academic researchers, pharmacy benefit managers, government agencies) to share the exact same content without restriction. Moreover, even where the information in issue rebuts, refines, or mitigates a labeled risk, the *Draft Guidance* outlines a number of stringent criteria that must be satisfied regarding the source of the information and the manner of distribution before manufacturers can avail themselves of the safe harbor. The First Amendment will not abide such content- and speaker-based distinctions. Finally, and as discussed in more detail in Part III, *infra*, the recommendations contained in the *Draft Guidance*

---

[16] *See, e.g.*, Citizen Petition, Docket No. FDA-2013-P-1079, at 6 (Sept. 3, 2013); Comments re: Scientific Exchange and Responses to Unsolicited Requests, Docket Nos. FDA-2011-N-0912 and FDA-2011-D-0868, at 4 (Mar. 27, 2012); Citizen Petition, Docket No. FDA-2011-P-0512, at 5 (July 5, 2011).

[17] *See Draft Guidance*, at 7 ("Any statements made by a representative of the firm to a recipient concerning the reprint should be consistent with its content and the information in the disclosure sheet.").

[18] *See, e.g.*, Letter from Leslie Kux, Assistant Commissioner for Policy, to Alan R. Bennett, Joan McPhee, Coleen Klasmeier, and Paul E. Kalb, Docket Nos. FDA-2011-P-0512 and FDA-2013-P-1079, 9 (June 6, 2014).

[19] *See e.g.*, *Virginia State Bd. of Pharm. v. Virginia Citizens Consumer Council, Inc.*, 425 U.S. 748, 756-57 (1976).

[20] *See, e.g.*, FDA, *Draft Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices* (Feb. 2014); FDA, *Draft Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices* (Dec. 2011).

are unconstitutionally vague and do not clearly delineate the boundaries between permitted and prohibited conduct.

II. The *Draft Guidance*'s Distinction Between Emerging Safety and Effectiveness Information

Although the *Draft Guidance* provides a pathway for manufacturers to communicate certain forms of emerging risk information, FDA has taken the position that effectiveness information—even if consistent with the product labeling—may not be shared by manufacturers unless supported by adequate and well-controlled studies.[21] FDA attempts to justify this distinction by describing differences in the "purpose, nature, and reliability" of safety and effectiveness data when evaluated in the context of market approval.[22] In particular, the Agency states that while evidence forming the basis for an effectiveness determination typically is intended to isolate the product's effect from other influences, the safety determination arises not from studies to test a specific safety hypothesis, but rather from a broad range of data sources relevant to how the product performs in the real world.[23]

We have described in previous submissions the problems with requiring the same quantum and quality of evidence for postmarket communications as is needed for market approval, and we will not reiterate those problems in significant detail here.[24] We emphasize today the fundamental inconsistency in FDA's approach of allowing risk information to be disseminated under the *Draft Guidance* while continuing to stifle the communication of effectiveness information. While we acknowledge that safety information may emerge from a variety of sources—including but not limited to spontaneous adverse event reports, observational studies, and meta-analyses—clinically relevant effectiveness information, too, can be gleaned from data obtained in the real world, as opposed to the controlled clinical trial setting. After a product has been on the market, newly emerging effectiveness information is routinely described in the medical literature; for example, data from extension phases of pivotal studies frequently feature in such publications, as do meta-analyses, retrospective analyses, comparative effectiveness research ("CER"), patient case studies, subgroup analyses, and other clinically relevant information. This wide body of information is more commonly available, can be based on larger sample sizes with a broader range of patients, and can be more up-to-date than data from randomized controlled clinical trials ("RCTs").

Even though such information may not meet the rigorous standard for inclusion in the product labeling, its value to health care decision-making is beyond dispute. Clinicians make prescribing decisions based on their professional judgment and a range of available information

---

[21] *See, e.g., Draft Guidance* at 2, 4 (describing the differences between the safety and effectiveness determinations in the context of market approval).
[22] *Id.*
[23] *Id.*
[24] *See, e.g.*, Comments, Draft Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses- Recommended Practices, Docket No. FDA-2008-D-0053 (May 2, 2014) ("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.") (citing 63 Fed. Reg. 64556, 64559 (Nov. 20, 1998))).

that goes well beyond the clinical trial data and other information on which FDA relied to approve a particular product. Prescribers may seek out observational data, for example, that sheds light on how patients with co-morbid conditions may fare when taking a drug, or how concurrent medication use may affect the drug's effectiveness. Third-party payers, moreover, approach the decision-making process from a particular perspective. Deliberative, inherently skeptical, and with an ever-increasing emphasis on the comparative value of a particular drug, payers regularly expect to see real-world data *in addition to* the RCT or other registration-quality data on which FDA approval was based. Indeed, in many respects, meta-analyses and observational studies are more valuable to payers in the assessment of cost, utilization, and effectiveness, because such evidence can be tailored to specific patient populations (*e.g.*, in a particular health plan), conditions of actual use (*e.g.*, the dose at which the drug is most commonly prescribed), and long-term outcomes (*e.g.*, for patients with chronic conditions), among other key variables not typically evaluated in RCTs. Under the current regulatory scheme, however, manufacturers—and only manufacturers—are not permitted to share this truthful and non-misleading information.

Dissemination of truthful, non-misleading effectiveness information as described above is no less critical to the public health than the timely communication of emerging safety information. Nevertheless, the safe harbor created by the *Draft Guidance* narrowly applies to the dissemination of safety information and indicates that the dissemination of effectiveness information will continue to be prohibited. This disparity hinders the free flow of valuable information to health care decision-makers and underscores the inadequacy of FDA's incremental approach to the regulation of manufacturer speech. As described in Part I, moreover, the distinctions between permitted and prohibited speech drawn by the Agency on the basis of the content and speaker are unconstitutional and are inappropriately grounded in FDA's view of what type of postmarket information may hold clinical value. Permitting manufacturers to disseminate emerging safety and effectiveness information, but requiring them to disclose any relevant limitations on the data, would be consistent with the First Amendment and would achieve the public health goal of ensuring that health care decision-makers have access to truthful, non-misleading information about medical products. We have described in a number of submissions the ways in which FDA could better align its regulatory scheme with the Constitution, which include not only the establishment of clear and unifying principles to govern manufacturer communications on the whole, but also specific proposals to facilitate the dissemination of truthful, non-misleading information about a product's effectiveness.[25] We accordingly urge FDA to reconsider its approach in the *Draft Guidance* and to permit more broadly the dissemination of emerging safety and effectiveness information.

III. Comments on Specific Recommendations in the *Draft Guidance*

The *Draft Guidance* sets forth numerous recommendations for manufacturers to consider before disseminating newly emerging risk information under the proposed safe harbor. We

[25] Comments, Draft Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses- Recommended Practices, Docket No. FDA-2008-D-0053 (May 2, 2014); Citizen Petition, Docket No. FDA-2013-P-1079, at 6 (Sept. 3, 2013); Comments re: Scientific Exchange and Responses to Unsolicited Requests, Docket Nos. FDA-2011-N-0912 and FDA-2011-D-0868, at 4 (Mar. 27, 2012); Citizen Petition, Docket No. FDA-2011-P-0512, at 5 (July 5, 2011).

described in Part I, above, the constitutional prohibition on imposing content- and speaker-based restrictions on manufacturer speech, as well as the government's burden to delineate the boundaries of permissible and impermissible conduct with precision. Below, we comment on specific recommendations in the *Draft Guidance*.

The *Draft Guidance* provides a number of criteria that must be satisfied before qualifying for dissemination under the safe harbor. These criteria require that the studies or analyses:

- Be "sufficiently well-designed and informative to merit consideration in assessing the implications of a risk[;]"[26]
- Be "at least as persuasive as" data that underlie the existing risk assessment; and
- "[G]ive appropriate weight and consideration to, and should be a fair characterization of, all relevant information in the safety database[.]"

Each of the terms provided above is undefined in the *Draft Guidance*, inherently subjective, and may be difficult for manufacturers to apply in practice. The requirement, for example, that a study be "sufficiently well-designed and informative to merit consideration" has not been further elucidated in the *Draft Guidance* and necessarily depends on a subjective assessment of the study, its purposes, and its conclusions. Subjective value judgments cannot form the basis for the availability of a safe harbor; after all, considering the varied informational needs of prescribers and payers, it is likely that even the recipients of emerging risk information may disagree as to its value. The requirement that a study be "at least as persuasive" as data sources that underlie the existing risk information—meaning the information found in the product labeling—is similarly subjective and depends on the professional judgment of the recipient. It also undermines the fundamental aim of the *Draft Guidance*, which is to ensure that health care decision-makers have timely access to emerging risk information. By its terms, the *Draft Guidance* would prohibit manufacturers from sharing risk information (*e.g.*, a new safety signal) grounded in preliminary data or analyses—even if the manufacturer explicitly indicated that it was preliminary and should be evaluated in the context of other available information. Finally, it is unlikely that many peer-reviewed articles are written in a way that satisfies the requirement that the publication be a "fair characterization of all relevant information in the safety database, including contrary or otherwise inconsistent findings."[27] Not only is this term subjective, but as a practical matter, it could operate to prevent the dissemination of studies and analyses that focus on a particular demographic subgroup (*e.g.*, geriatric women), are drawn from a particular patient population (*e.g.*, a patient registry in Denmark), or are limited to the use of a drug in only one of its approved indications. Moreover, given the broad range of safety data available for a drug, and the proprietary nature of some of that information, authors and investigators simply may lack access to "all relevant information" about a product's safety profile.

Prescribers, payers, and other health care stakeholders may find value in studies or analyses even if the information fails to satisfy FDA's onerous criteria for dissemination under the *Draft Guidance*. Furthermore, because the *Draft Guidance* is non-binding and the dissemination criteria do not clearly delineate which information may be shared by

[26] *Draft Guidance*, at 6.
[27] *Id.* at 7.

manufacturers, it is likely that manufacturers will err on the side of caution and under-communicate clinically relevant information as envisioned in the *Draft Guidance*. This lack of precision raises serious issues under the First and Fifth Amendments and leaves manufacturers who may fail to interpret the criteria consistently with FDA's expectations exposed to enforcement actions or other sanctions. Rather than prohibiting the dissemination of publications that fail to satisfy these safe harbor requirements, the Agency should instead affirmatively permit manufacturers to distribute a broader range of studies and analyses so long as the design and limitations are clearly disclosed.

We appreciate the opportunity to comment.

Respectfully submitted,

Alan R. Bennett
ROPES & GRAY LLP
One Metro Center
700 12th Street, NW
Washington, DC 20005
Telephone: (202) 508-4604
Facsimile: (202) 383-8327
alan.bennett@ropesgray.com

Coleen Klasmeier
SIDLEY AUSTIN LLP
1501 K Street, NW
Washington, DC 20005
Telephone: (202) 736-8000
Facsimile: (202) 736-8711
cklasmeier@sidley.com

Joan McPhee
ROPES & GRAY LLP
Prudential Tower
800 Boylston Street
Boston, MA 02199-3600
Telephone: (617) 951-7535
Facsimile: (617) 235-0412
joan.mcphee@ropesgray.com

Paul E. Kalb
SIDLEY AUSTIN LLP
1501 K Street, NW
Washington, DC 20005
Telephone: (202) 736-8000
Facsimile: (202) 736-8711
pkalb@sidley.com

Counsel to the Medical Information Working Group