SIDLEY ROPES & GRAY

January 5, 2024

VIA ELECTRONIC SUBMISSION

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

Re: Revised Draft Guidance for Industry: "Communications From Firms to Health Care Providers Regarding Scientific Information on Unapproved Uses of Approved/Cleared Medical Products" (Docket No. FDA-2008-D-0053)

The Medical Information Working Group ("MIWG") submits these comments to address the revised draft guidance for industry, *Communications From Firms to Health Care Providers Regarding Scientific Information on Unapproved Uses of Approved/Cleared Medical Products: Questions and Answers* (the "Revised Draft"), which was recently issued by the U.S. Food and Drug Administration ("FDA" or "the Agency").

INTRODUCTION

MIWG is a coalition of firms engaged in innovative medical product research and development. The group was formed to seek clarity in the FDA regulatory scheme regarding dissemination of truthful, non-misleading information about prescription drugs, biological products, and medical devices, and to improve the regulatory and enforcement environment affecting communications regarding medical products. This includes communications about products in development and new uses of marketed products.[1]

Over the past 15 years, MIWG has made numerous submissions to FDA addressing the regulatory framework for communications by research and development firms, including, among other issues, the public health value of truthful, non-misleading information regarding unapproved uses, the scope of FDA's legal authority to regulate communications, and the constitutional implications of FDA's approach to regulation.[2] In 2014, FDA responded to two MIWG citizen petitions by committing to a "comprehensive review of its regulations and guidance documents to harmonize the goal of protecting the public health with First Amendment interests."[3] FDA also committed to issuing guidance that addresses "manufacturer discussion regarding scientific information more generally" than what is covered by the Revised Draft.[4]

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[1] The members of the MIWG are: Amgen, Inc.; Bayer Healthcare Pharmaceuticals, Inc.; Bristol-Myers Squibb Company; Eli Lilly and Company; GlaxoSmithKline, LLC; Johnson & Johnson; Novartis Pharmaceutical Corp.; Pfizer Inc.; and Regeneron Pharmaceuticals, Inc.

[2] The MIWG's prior submissions to FDA are available at www.miwg.org.

[3] *See* Citizen Petition Approval Response from FDA CDER to Ropes & Gray LLP and Sidley Austin LLP, Docket Nos. FDA-2011-P-0512, FDA-2013-P-1079, at 8, 9 (June 6, 2014).

[4] *Id.* at 9.

MIWG previously submitted comments regarding two other draft versions of guidance on this topic,[5] and we appreciate the opportunity to submit these comments on the Revised Draft.

COMMENTS ON THE REVISED DRAFT

I. BACKGROUND AND OVERVIEW

The Revised Draft addresses a topic of significant importance to public and individual health—the communication of scientific information on unapproved uses of approved or cleared medical products ("SIUU communications").[6] The Revised Draft is also the latest development in a long arc of legal and regulatory history—this topic has been the subject of prior FDA policy,[7] legislation,[8] rulemaking,[9] and litigation,[10] in addition to a final guidance issued in 2009 and a previous revised draft issued in 2014.[11]

MIWG appreciates FDA's renewed attention to guidance development in this area. MIWG also appreciates FDA's explicit statements in the Revised Draft that SIUU communications may involve sharing of materials from independent clinical practice resources and firm-generated presentations of scientific information from an accompanying published reprint. We also appreciate FDA's explicit recognition that SIUU communications may be shared through various media, platforms, and venues, such as digital media, websites, and online

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[5] MIWG Comments, Draft Guidance: 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) [hereinafter *MIWG Comment on 2008 Draft Guidance*]; MIWG 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).

[6] Throughout these comments, the term "SIUU" refers to scientific information on unapproved use(s) of approved/cleared medical products and the term "SIUU communication" refers to a communication that involves sharing of a published scientific or medical journal article ("reprint"), published clinical reference resource (*i.e.*, a clinical practice guideline ("CPG"), scientific or medical reference text, and/or materials from an independent clinical practice resource), and/or a firm-generated presentation of scientific information from an accompanying published reprint, with disclosure of "all information necessary for HCPs to interpret the strengths and weaknesses and validity and utility of the information in the ... communication." *See, e.g.*, Revised Draft at 6, 12. This is generally consistent with the use of the term "SIUU Communication" in the Revised Draft, subject to the concerns with the Revised Draft discussed in these comments.

[7] 61 Fed. Reg. 52800 (Oct. 8, 1996).

[8] Food and Drug Administration Modernization Act, Pub. L. 105-115, § 401, 111 Stat. 2296, 2356 (1997).

[9] 63 Fed. Reg. 64556 (Nov. 20, 1998) (codified at 21 C.F.R. part 99).

[10] *See, e.g.*, *Washington Legal Found. v. Kessler*, 880 F. Supp. 26 (D.D.C. 1995); *Washington Legal Found. v. Henney*, 202 F.3d 331 (D.C. Cir. 2000), *vacating* 13 F. Supp. 2d 51 (D.D.C. 1998) (*as amended by* 36 F. Supp. 2d 16 (D.D.C. 1999) *and* 36 F. Supp. 2d 418 (D.D.C. 1999)) *and* 56 F. Supp. 2d 81 (D.D.C. 1999), *remanded to* 128 F. Supp. 2d 11 (2000); 65 Fed. Reg. 14,286 (Mar. 16, 2000).

[11] *Revised Draft Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices* (Feb. 2014), https://www.fda.gov/media/88031/download [hereinafter *2014 Revised Draft Guidance*]; *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* (Jan. 2009), https://www.regulations.gov/document/FDA-2008-D-0053-0127 [hereinafter *2009 Final Guidance*].

platforms, as well as poster sessions, commercial exhibit halls, and similar venues at medical or scientific conferences.

As responsible, research-driven firms committed to advancing science and improving patient care, the members of MIWG fully agree with FDA that SIUU communications should serve applicable public and individual health interests and, in the words of the Revised Draft, be "truthful, non-misleading, factual, and unbiased," including because they are accompanied by all contextual information needed for health care professionals ("HCPs") "to interpret the strengths and weaknesses and validity and utility of the information about the unapproved use."[12] We also agree that SIUU communications should be based on materials that have been subject to robust review by organizations and individuals with relevant scientific expertise, under processes addressing conflicts of interest.[13] These parameters help ensure that SIUU communications are non-promotional and appropriately understood by HCPs.

The recommendations in the Revised Draft, however, far exceed these appropriate parameters. In so doing, they fail to serve the applicable public and individual health interests and exceed the statutory and constitutional limits on the Agency's authority to restrict the communication of truthful, non-misleading, scientific information. Moreover, certain concepts, standards, and definitions introduced in the Revised Draft are ambiguous and untethered to the applicable statutory and regulatory authorities. They also add significant complexity and inconsistency to a regulatory regime that is already disjointed, overreaching, and rife with numerous unanswered questions. Overall, the Revised Draft reflects continued policymaking in a piecemeal and incomplete way that does not promote clarity regarding communications by firms engaged in innovative medical product research and development.

As a result, the Revised Draft is likely to chill a significant amount of truthful and non-misleading communication regarding unapproved uses, despite a recognized need for HCPs to receive and participate in dialogue regarding this information.[14] To avoid this, and to address the statutory and constitutional issues implicated by the Revised Draft, MIWG urges FDA to make substantial revisions.

Most critically, we ask FDA to acknowledge the full range of public and individual health interests served by SIUU communications and to reconsider its attempt to dictate what studies and analyses may be considered "scientifically sound" and "clinically relevant" by practicing HCPs, where SIUU may be used by them to inform clinical practice decisions. The current approach improperly substitutes FDA's views for those of HCPs and, importantly, is patently contrary to what experts would deem appropriate in this context. We also request that FDA

[12] *See, e.g.*, Revised Draft at 2, 8-9, 12.

[13] *See, e.g.*, *id.* at 20 (addressing conflict of interest for reprints), 23 (same for CPGs), 24-25 (same for reference texts and independent clinical practice resources).

[14] Beyond this, MIWG believes that FDA fundamentally lacks authority to initiate enforcement against a firm based upon SIUU communications that are truthful, non-misleading, factual, and unbiased, and that it would be contrary to the relevant public and individual health interests for FDA or others to try to do so. There is nonetheless a risk that the government might attempt such enforcement, so the guidance will deter a significant amount of these communications. *See, e.g.*, 65 Fed. Reg. at 14287 (asserting that non-compliance with an FDA "safe harbor" policy regarding communications may result in "FDA ... bring[ing] an enforcement action under the FDCA").

implement other more targeted revisions to address relevant issues and to achieve greater clarity.

The following comments explain in more detail how the "enforcement policy" described in the Revised Draft would, in general, be highly problematic from a public and individual health perspective (section II.A), contradict the applicable statutory and constitutional requirements (sections II.B and II.C), and reflect a piecemeal and incomplete approach that does not promote overall clarity regarding communications by research and development firms (section II.D). We also provide examples of specific ways in which the document should be revised and request a new comment period before any responsive changes result in issuance of a final guidance (section III).

II. OVERARCHING ISSUES RAISED BY THE REVISED DRAFT

A. The Revised Draft fails to serve the applicable public and individual health interests.

It is well established that unapproved uses of medical products are a legitimate aspect of appropriate medical practice, especially in the settings of oncology, dermatology, psychiatry, many rare diseases, and pediatric medicine.[15] For example, "FDA has long recognized that in certain circumstances, new (off-label) uses of approved products are appropriate, rational, and accepted medical practice. There are important off-label uses of approved products."[16] FDA also recognized in the 2009 final guidance that "off-label uses or treatment regimens ... may even constitute a medically recognized standard of care."[17] Indeed, this is the case in many disease areas.

It is also well established that SIUU communications can serve many public and individual health interests other than informing clinical practice decisions about unapproved uses. These include the general importance of sharing information about unapproved uses and interests in furthering scientific understanding and research, as described in further detail below.

There are many sources of information about unapproved uses, but not all HCPs have the time and resources to find it.[18] Accordingly, limitations on communication of this information

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[15] *See, e.g.*, *MIWG Comments on 2008 Draft Guidance*, *supra* note 5, at 3-4 ("It has long been recognized that off-label use in oncology is widespread.... A 2002 study ... determined that drugs were used off-label for every evaluated diagnosis in dermatologic disease.... Approximately 90 percent of patients with rare diseases are prescribed at least one drug for an off-label use."); Rusz CM, et al., *Off-Label Medication: From a Simple Concept to Complex Practical Aspects*, Int J Environ Res Public Health, 2021 Oct 4, 18(19):10447 (noting that off-label practice is widespread in rare diseases, oncology, and psychiatry (especially in pediatric and elderly populations)), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8508135/.

[16] 63 Fed. Reg. 31143, 31153 (June 8, 1998).

[17] *2009 Final Guidance*, *supra* note 11, at 3.

[18] *See, e.g.*, O'Reilly J & Dalal A, *Off-Label or Out of Bounds? Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs*, Ann Health Law, 2003 Summer, 12(2):295-324 ("It is nearly impossible for a physician to read all of the medical journals and compendia available, especially given the proliferation of medical reading materials, both hard copy and on the internet, in the last decade alone."), https://pubmed.ncbi.nlm.nih.gov/12856461/; Ventola CL, *Off-Label Drug Information: Regulation, Distribution, Evaluation, and Related Controversies*, P T, 2009 Aug, 34(8):428-40 ("It is extremely difficult

by innovative research and development firms may significantly impair the ability of HCPs to obtain important information that they need and want.[19]

Any further drafts of the guidance should therefore appropriately account for all the public and individual health interests that can be advanced by SIUU communications and should appropriately serve those interests. Unfortunately, the Revised Draft does neither.

1. The Revised Draft recognizes only an HCP interest in SIUU to inform clinical practice decisions for the care of an individual patient, which is much narrower than the full range of applicable interests, including those FDA has previously recognized.

The Revised Draft repeatedly states that it reflects an effort to "strike a careful balance, supporting HCP interest in scientific information about unapproved uses of approved/cleared medical products *to inform clinical practice decisions for the care of an individual patient*."[20] It also states that its recommendations "are specific to communications by firms *to HCPs engaged in making clinical practice decisions for the care of an individual patient*,"[21] and emphasizes that an underlying study or analysis must be "clinically relevant," which it defines as able to "provide information that is relevant to *HCPs engaged in making clinical practice decisions for the care of an individual patient*."[22]

This all reflects a focus on a limited subset of scenarios that is much narrower than the full range of scenarios for which HCPs may need and want SIUU.

Indeed, FDA has long recognized that truthful and non-misleading SIUU communications are *generally* important, regardless of whether they may inform a specific clinical practice decision. For example, in 1998, the Agency expressly acknowledged the "public health gains associated with the earlier dissemination of objective, balanced, and accurate information" about unapproved uses.[23] And, in prior iterations of this guidance, FDA recognized that "the public health can be served when health care professionals receive truthful and non-

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for a physician to independently keep current by reading all of the medical journals and compendia available."), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2799128/; 143 Cong. Rec. S8162, S8166 (daily ed. July 28, 1997) (statement of Sen. William Frist, quoting Dr. Lindberg at the National Library of Medicine) ("But to be honest with you, your typical physician is so busy today delivering care, it is very unlikely that they are going to sit down at a computer terminal ... and go to the Internet and get information.... 'If a conscientious doctor were to read two medical articles before retiring every night, he would have fallen 550 years behind in his reading at the end of the first year.'").

[19] *See, e.g.*, *21st Century Cures: Examining Barriers to Ongoing Evidence Development and Communication: Hearing Before the Subcomm. on Health of the H. Energy and Com. Comm.,* 113th Cong. 42 (2014) (testimony for the record of Gregory Schimizzi, Cofounder, Coalition of State Rheumatology Organizations) ("By limiting the sharing of information [about approved and medically accepted alternative uses of FDA-approved medicines by pharmaceutical companies], physicians are hampered in their ability to access all available sound medical evidence and firm scientific rationale necessary to treat patients with difficult problems.").

[20] *See, e.g.*, Revised Draft at 2, 9, 14, 17 (emphasis added).

[21] *Id.* at 6 (emphasis added).

[22] *See, e.g.*, *id.* at 2 (emphasis added).

[23] 63 Fed. Reg. at 64579; *see also* 63 Fed. Reg. at 31153 (same).

misleading scientific and medical information on unapproved uses of approved or cleared medical products," full stop.[24]

FDA has also recognized that SIUU communications may advance public and individual health interests by furthering scientific understanding and research. As the Agency stated in 2017:

> [R]eliable scientific information regarding unapproved uses may help further scientific research, such as through hypothesis generation, and increasing scientific understanding in new and developing areas. Making the data and information public may also encourage the collection of outcomes through surveillance and reporting, stimulate appropriate additional evidence generation, and identify unapproved uses that are likely to present an unreasonable risk to patients. Sharing information may also allow for collaborative efforts to develop new treatments or improve existing ones.[25]

And this only scratches the surface of how communications with HCPs about emerging data can further innovation. Robust conversations between those conducting research and practicing HCPs are critical to the development and understanding of medical science.

It appears that the Revised Draft may reflect a deliberate choice by FDA to account for these benefits regarding scientific understanding and research solely through proposed development of a separate policy on communication of SIUU to "HCPs in their capacities as researchers."[26] This is inappropriate because the benefits described above do not apply solely to communication of SIUU to "researchers." Rather, in FDA's own words quoted above, communication of SIUU to HCPs in *any* function fosters their involvement in "collection of outcomes through surveillance and reporting," identifying needs for "appropriate additional evidence generation," identifying "unapproved uses that are likely to present an unreasonable risk to patients," and engaging in "collaborative efforts to develop new treatments or improve existing ones."

In sum, limiting truthful, non-misleading, factual, and unbiased SIUU communications to scenarios where it may inform clinical practice decisions would be unduly restrictive and adversely impact public and individual health. MIWG is aware of no new developments that should compel FDA to abandon its prior recognition of the full range of benefits associated with such communications.

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[24] *2009 Final Guidance*, *supra* note 11, at 6; *see also 2014 Revised Draft Guidance*, *supra* note 11, at 6 ("this draft guidance, like the 2009 guidance, recognizes the value to health care professionals of truthful and non-misleading scientific or medical publications on unapproved new uses").

[25] *FDA Memorandum: Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products*, at 17-18 (Jan. 2017), https://www.regulations.gov/document/FDA-2016-N-1149-0040 [hereinafter *2017 Memorandum*].

[26] *See, e.g.*, Revised Draft at 6 n.11; *see also* 88 Fed. Reg. 73031, 73033 (Oct. 24, 2023) (requesting comments on "What considerations, if any, exist that are unique to communications of scientific information about unapproved use(s) of approved/cleared medical products by firms to researchers (including HCPs working in their capacity as researchers)?").

2. FDA's attempt to impose its own views of what studies and analyses are "scientifically sound" and "clinically relevant" fails to support even the inappropriately narrow interest in SIUU to inform clinical practice decisions.

Even more problematic than the concern described above is the Revised Draft's attempt to dictate the circumstances under which studies and analyses that serve as the basis for an SIUU communication may be considered "scientifically sound" and "clinically relevant." This substitutes FDA's own views for those of practicing HCPs and is demonstrably contrary to the views of relevant clinical experts. For all these reasons, the approach is inappropriate.

To be clear, MIWG does not object to the "scientifically sound" and "clinically relevant" concepts as they might be understood by practicing HCPs. We have no intention to engage in communications based on studies or analyses without regard to whether they are scientifically sound or clinically relevant, or without the context needed for practicing HCPs to make their own judgments about the validity and utility of the information. This would not further our goal of scientific innovation or contribute positively to patient care.

We are very concerned, however, that FDA's approach inappropriately takes into account *only* an interest in SIUU to inform clinical practice decisions, disregarding other vital interests discussed above. With respect to those other interests, relevant studies and analyses need not always be "scientifically sound" and "clinically relevant." For example, it may be important to discuss nonclinical or early phase data with HCPs in order to determine what additional studies or analyses might or might not be needed to inform clinical practice decisions.

Even with respect to the interest in informing clinical practice decisions, moreover, FDA's approach in the Revised Draft is flatly inconsistent with the Agency's own longstanding recognition that *individual HCPs*—not the Agency—are responsible for making prescribing decisions about unapproved uses based on the information *they* deem scientifically sound and clinically relevant. For example, the Agency has stated:

- "[FDA] is charged with the responsibility for judging the safety and effectiveness of drugs and the truthfulness of their labeling. *The physician is then responsible* for making the final judgment as to which, if any, available drugs a patient will receive in light of the information set forth in their labeling and other adequate scientific data available."[27]

- "*If physicians use a product for an indication not in the approved labeling, they have the responsibility* to .... base its use on firm scientific rationale and on sound medical evidence ...."[28]

We are also very concerned that FDA's execution of its approach appears to be highly restrictive and inconsistent with what relevant experts would deem appropriate in this context.

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[27] 37 Fed. Reg. 16503, 16504 (Aug. 15, 1972) (emphasis added).

[28] *Guidance for Institutional Review Boards and Clinical Investigators: "Off-Label" and Investigational Use Of Marketed Drugs, Biologics, and Medical Devices* (Jan. 1998) (emphasis added), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/label-and-investigational-use-marketed-drugs-biologics-and-medical-devices.

As a starting point, the language of the draft lacks clarity and could be read to suggest that SIUU communications should be made only where the underlying studies or analyses are so reliable that they would meet the requirements for full FDA authorization of a new use. The Revised Draft states broadly that "well-designed and well-conducted trials" are "able to generate scientifically sound and clinically relevant information,"[29] but the examples that FDA provides, as well as other language in the Revised Draft, suggest that the Agency may in practice apply an exceedingly high bar.

For example, the Revised Draft points to "randomized, double-blind, concurrently controlled superiority trials" ("RCTs") as "the most likely to provide scientifically sound and clinically relevant information."[30] Similarly, while FDA acknowledges that certain real-world evidence ("RWE") and real-world data ("RWD") could appropriately support SIUU communications, it suggests that firms evaluate RWE/RWD by reviewing Agency guidance describing when such data could appropriately support medical product authorization.[31] Further, the Revised Draft states, nearly categorically, that "early stage" data, such as data from Phase 2 studies, are "unlikely to be sufficiently reliable by themselves to allow for a determination of clinical relevance. As a result, a communication based on this type of data alone is unlikely to be within the scope of the enforcement policy outlined in this guidance."[32]

Overall, the concepts articulated in the Revised Draft, when read in conjunction with the examples FDA provides, appear to mimic in material respects the standards for authorization of new medical products, such as the "substantial evidence" and "adequate and well-controlled" standards for new drug approval, as defined and implemented by FDA.[33]

This reflects a highly restrictive, paternalistic approach that is contrary to what relevant experts would deem appropriate. To illustrate, consider a review of the National Comprehensive Cancer Network ("NCCN") guidelines, which are recognized as the most comprehensive and widely used standards for care, coverage, reimbursement, and quality improvement initiatives in oncology.[34] The vast majority of therapeutic recommendations in the NCCN guidelines are

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[29] Revised Draft at 10.

[30] *Id.*

[31] *Id.* at 10-11 & n.23; *Guidance for Industry and Food and Drug Administration Staff: Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices* (Aug. 2017), https://www.fda.gov/media/99447/download; *Guidance for Industry: Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products* (Aug. 2023), https://www.fda.gov/media/171667/download.

[32] Revised Draft at 11-12 & n.26-28.

[33] *See, e.g.*, 21 U.S.C. § 355(d); 21 C.F.R. § 314.125(b)(5).

[34] Poonacha TK & Go RS, *Level of Scientific Evidence Underlying Recommendations Arising from the National Comprehensive Cancer Network Clinical Practice Guidelines*, J Clin Oncol, 2011 Jan 10, 29(2):186-91 ("NCCN guidelines are the most comprehensive and widely used oncology standard in clinical practice in the world. Recommendations found in NCCN guidelines are now accepted by the Centers for Medicare and Medicaid Services and most private insurance companies."), https://pubmed.ncbi.nlm.nih.gov/21149653/; Wagner J, et al., *Frequency and Level of Evidence Used in Recommendations by the National Comprehensive Cancer Network Guidelines Beyond Approvals of the US Food and Drug Administration: Retrospective Observational Study*, BMJ, 2018 Mar 7, 360:k668 ("The NCCN is a prominent set of cancer specific guidelines used in clinical practice and now serves as one of five compendiums for private insurer and the Centers for Medicare and Medicaid Services (CMS)

based on evidence *other than* RCTs, including data from indirect comparisons among randomized trials, phase 2 or non-randomized trials, limited data from multiple smaller trials, and retrospective studies.[35] Indeed, published analyses of the guidelines have consistently reported that at least 80% of all therapeutic recommendations in the NCCN guidelines are based on data other than RCTs.[36] The guidelines nonetheless generally reflect expert consensus of what constitutes appropriate treatment in the oncology setting, based on data that is undoubtedly "scientifically sound" and "clinically relevant," according to the experts who have reviewed this information and the HCPs who rely on it.[37]

In other words, the Revised Draft's emphasis on the importance of "randomized, double-blind, concurrently controlled superiority trials"[38] when describing the "scientifically sound" and "clinically relevant" concepts goes well beyond how the medical community understands these concepts and would significantly limit the dissemination of information that HCPs need and want.

In addition, the Revised Draft is inconsistent with FDA's own approach to evaluating the reliability of data about medical products in general, as well as its past statements about use of such data to inform clinical practice decisions involving unapproved uses. For example, FDA itself has previously approved products based on Phase 2 data,[39] and the Agency currently

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coverage"), https://pubmed.ncbi.nlm.nih.gov/29514787/; Kurzrock R, et al., *Level of Evidence Used in Recommendations by the National Comprehensive Cancer Network (NCCN) Guidelines Beyond Food and Drug Administration Approvals*, Ann Oncol, 2019 Oct, 30(10):1647-52 ("The NCCN Drugs & Biologics Compendium (NCCN Compendium) is widely recognized by public and private insurers alike as an authoritative reference to guide oncology coverage decisions."), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6857604/; Desai AP, et al., *Category of Evidence and Consensus Underlying National Comprehensive Cancer Network Guidelines: Is There Evidence of Progress?*, Int J Cancer, 2021 Jan 15, 148(2):429-36 ("These guidelines which include clinical recommendations for over 65 types of cancers, supportive care practice patterns and screening, are well regarded as the oncology standard in clinical practice, insurance reimbursements and quality improvement initiatives in oncology around the globe."), https://pubmed.ncbi.nlm.nih.gov/32674225/.

[35] As NCCN states: "Large, well designed, randomized controlled trials (RCTs) may provide high-quality clinical evidence in some tumor types and clinical situations. However, *much of the clinical evidence available to clinicians is primarily based on data from indirect comparisons among randomized trials, phase II, or non-randomized trials, or in many cases, on limited data from multiple smaller trials, retrospective studies, or clinical observations.* In some clinical situations, no meaningful clinical data exist and patient care must be based upon clinical experience alone." *Development and Update of Guidelines*, NCCN (last accessed Dec. 19, 2023) (emphasis added), https://www.nccn.org/guidelines/guidelines-process/development-and-update-of-guidelines.

[36] *See, e.g.*, Poonacha & Go, *supra* note 34 (reporting that only 6% of therapeutic recommendations in reviewed NCCN guidelines were designated as "Category 1", which reflects support from large, well-designed RCTs); Wagner et al., *supra* note 34 (reporting 16%); Kurzrock et al., *supra* note 34 (in-depth re-analysis of the data reviewed by Wagner et al.); Desai et al., *supra* note 34 (reporting 7%).

[37] *See, e.g.*, *Development and Update of Guidelines*, *supra* note 35 (noting that Category 2A and 2B recommendations are based on "lower-level evidence," meaning evidence other than large, well-designed RCTs, and still reflect "NCCN consensus that the intervention is appropriate").

[38] Revised Draft at 10.

[39] One example is XALKORI (crizotinib), which was originally approved by FDA in 2011 based on phase 2 data. *See, e.g.*, Cross-Discipline Team Leader Review for NDA 202570, at 2 (July 12, 2011) ("This application includes 2 single arm trials, one from this Phase 2 extension (Study B) and the other a single

emphasizes the importance of communicating early-stage data among practicing HCPs, for example, through the multi-agency collaborative CURE ID program. FDA describes CURE ID as "a resource for physicians to share information where no FDA-approved product proven to be safe and effective exists for the new use," with no limitation on the type or quality of information that may be shared.[40] All of this strongly undermines the suggestion in the Revised Draft that early-stage data are "unlikely" to allow for a determination of clinical relevance.[41]

Further, FDA and others have recognized that there are situations where RCTs are impractical (or even unethical) and unnecessary, including those involving rare diseases where there is significant unmet need.[42] And, in the prior policy statements described above, FDA long ago made clear that individual HCPs can, *and should*, make prescribing decisions about unapproved uses based on "adequate scientific data," a "firm scientific rationale" and/or "sound medical evidence"[43]—*i.e.*, information that, in general, may not align with the demanding views articulated in the Revised Draft.

As a result, FDA's approach appears to undermine the stated interest of the Revised Draft, including by discouraging SIUU communications in situations where they are needed most. For example, the Revised Draft explicitly recognizes that an HCP's interest in SIUU to inform clinical practice decisions is especially significant when "there is no medical product that is a proven treatment."[44] At the same time, however, the Revised Draft appears to strongly discourage SIUU communications in this scenario, given the discussion suggesting that they should be made only where the underlying studies or analyses are so reliable that they

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arm, Phase 2 trial (Study A)."), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202570Orig1s000CrossR.pdf.

[40] CURE ID App Lets Clinicians Report Novel Uses of Existing Drugs, FDA (current as of June 8, 2020), https://www.fda.gov/drugs/science-and-research-drugs/cure-id-app-lets-clinicians-report-novel-uses-existing-drugs.

[41] Revised Draft at 12.

[42] *See, e.g.*, *Guidance for Industry: Rare Diseases: Considerations for the Development of Drugs and Biological Products* 10-12 (Dec. 2023) ("in certain rare disease development programs ... there may be situations where it would be reasonable to explore flexibility in clinical investigation design"; "if there is a well-defined, predictable natural history and if the therapeutic product has a large treatment effect on an objective and reliably measured biomarker or clinical endpoint ... flexibility in design should be considered"), https://www.fda.gov/media/136058/download; *Guidance for Industry: Slowly Progressive, Low-Prevalence Rare Diseases With Substrate Deposition That Result From Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies* 2 (Mar. 2020) ("In rare circumstances, conducting clinical trials may be impossible because of the extremely low number of patients with a specific disease or with a clinical manifestation of interest for a given disease."), https://www.fda.gov/media/136058/download; *CIOMS International Ethical Guidelines for Health-Related Research Involving Humans* 16 (2016) ("Although conventional randomized controlled clinical trials are often considered the gold standard, other study designs such as response-adaptive trial designs, observational studies, or historical comparisons can also yield valid research results. Researchers and sponsors must carefully consider whether the research question can be answered with an alternative design, and whether the risk-benefit profile of alternative designs is more favourable when compared to a conventional randomized controlled trial."), https://cioms.ch/publications/product/international-ethical-guidelines-for-health-related-research-involving-humans/.

[43] *See supra* notes 27-28 and accompanying text.

[44] Revised Draft at 8.

practically *do* prove the safety and efficacy of a treatment to the degree that would be required for FDA authorization.

Overall, the Revised Draft reflects an effort by FDA to substitute its own restrictive views of the "scientifically sound" and "clinically relevant" concepts for the views of practicing HCPs, which is an overreach that will deprive the medical community of important truthful, non-misleading, factual, and unbiased scientific information, all to the detriment of public and individual health interests recognized by FDA. Given the wide range of circumstances in which available data may be considered scientifically sound and clinically relevant by practicing HCPs, the better approach is to simply recommend that there be sufficient contextual information to enable those HCPs to assess SIUU communications for themselves, including material aspects of study design, methodology, and results, as well as any material limitations related to those aspects.

B. The Revised Draft exceeds the statutory limitations on FDA's authority because it incorrectly posits that FDA has authority over SIUU communications, which do not constitute "labeling," "advertising," or evidence of a new "intended use."

FDA's ability to regulate in this area is defined by the grant of statutory authority in the Federal Food, Drug, and Cosmetic Act ("FDCA"). Under the FDCA, the Agency's jurisdiction as it relates to communications by research and development firms extends only to the regulation of "labeling," the regulation of "advertising," and—based on FDA's interpretation of the statutory requirement that labeling bear adequate directions for use—considering evidence of "intended use."[45]

The Revised Draft does not meaningfully address how its proposed approach to regulation of truthful and non-misleading SIUU communications is consistent with these jurisdictional limitations and, to the contrary, it plainly conflicts with them.

As a starting point, the Revised Draft defines the term "SIUU communication," in key respects, as a communication of certain "scientific information" that provides "all information necessary for HCPs to interpret the strengths and weaknesses and validity and utility of the information in the ... communication."[46] It then states, as a matter of "enforcement policy," that "FDA does not intend to use such communication standing alone as evidence of a new intended use" if made "in a manner that is consistent with the recommendations in this guidance."[47] This suggests that FDA believes SIUU communications are inherently subject to FDA regulation and that any such communications inconsistent with or outside the scope of the Revised Draft may expose firms to enforcement.[48] However, FDA nowhere explains whether or how such communications would qualify as "labeling," "advertising," or evidence of "intended use," and therefore subject to enforcement under the applicable FDCA provisions.

MIWG has long raised concerns about how FDA interprets these and other related terms and has repeatedly requested that FDA clearly define the bounds of its regulatory authority with

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[45] *See, e.g.*, 21 U.S.C. §§ 352(a), (f)(1), (n); 21 C.F.R. §§ 201.5, 201.100, 201.128, 202.1.

[46] Revised Draft at 6, 12-14.

[47] *Id.* at 3.

[48] *Id.*

respect to communications in a way that is consistent with statutory and constitutional limitations.[49] Imprecision in the Agency's interpretation of key regulatory concepts—including labeling, advertising, promotion, evidence of intended use, and scientific exchange—persists in the Revised Draft, will exacerbate confusion among regulated industry, and will deter the communication of important, truthful, and non-misleading information.

Regardless, truthful, non-misleading, factual, and unbiased SIUU communications plainly do not constitute "labeling," as that term is properly construed. As MIWG has repeatedly emphasized, under the law, not all "written, printed, or graphic matter" that is merely textually related to a medical product qualifies as labeling. Rather, the material must satisfy various functional criteria, including by supplementing or explaining the product and otherwise being "interdependent" with the relevant product.[50]

Nor do such communications constitute "advertising" or "promotion." FDA has never defined those terms, despite their importance and a need to do so previously highlighted by MIWG.[51] Nevertheless, FDA explicitly refers to SIUU communications as "scientific" and makes various statements plainly distinguishing such communications from promotional communications, underscoring that they are not subject to FDA regulation as advertising.[52]

Finally, these communications do not constitute evidence of "intended use," and the Revised Draft makes no effort to establish otherwise. Instead, it simply asserts that intended use can be established from a medical product's "label, accompanying labeling, promotional claims, advertising, and any other relevant source," and that "claims or statements made by or on behalf of a firm that explicitly or implicitly *promote* a medical product for a particular use may be taken into account."[53] Even this overbroad, problematic interpretation of intended use, which

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[49] *See, e.g.*, MIWG Comments, Draft Guidance: Prescription Drug-Use-Related Software, Docket No. FDA-2018-N-3017, at 2 (Jan. 22, 2019); MIWG, White Paper: Systemic, Society, and Legal Developments Require Changes to FDA's Regulation of Manufacturer Speech, Docket No. FDA-2013-P-1079, at 42-46 (Oct. 31, 2014) [hereinafter *MIWG 2013 White Paper*]; MIWG, Citizen Petition, Docket No. FDA-2013-P-1079, at 13-15 (Sept. 3, 2013) [hereinafter *MIWG 2013 Citizen Petition*].

[50] *See e.g.*, MIWG Comments, Regulatory Considerations for Prescription Drug Use- Related Software Guidance for Industry, Docket No. FDA-2023-D-2482, at 3-4, 7-10 (Dec. 18, 2023); *MIWG 2013 Citizen Petition*, *supra* note 49, at 9-10; *MIWG 2013 White Paper*, *supra* note 49, at 42-46.

[51] *See, e.g.*, MIWG, Citizen Petition, Docket No. FDA-2011-P-0512, at 5 (July 5, 2011) ("FDA policies may be difficult to interpret due to the use of ambiguous language and undefined terms like 'promotion' and 'scientific exchange.'"); MIWG, Comments, Scientific Exchange and Responses To Unsolicited Requests, Docket Nos. FDA- FDA-2011-D-0868, 2011-N-0912, at 2 (Mar. 27, 2012) ("FDA should focus its efforts on clarifying the scope of key statutory provisions, such as the 'labeling' and 'advertising' definitions, that determine the extent of the agency's regulatory authority"); *MIWG 2013 Citizen Petition*, *supra* note 49, at 15 ("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.").

[52] *See, e.g.*, Revised Draft at 17 (recommending that "firms avoid sharing an SIUU communication for a medical product together with a promotional communication for that product for its approved use(s) because combining these two types of communications is more likely to lead to conflation of the approved use and unapproved use information," and recommending that "firms use dedicated vehicles, channels, and venues for sharing SIUU communications that are separate from the vehicles, channels, and venues used for promotional communications about approved uses").

[53] *Id.* at 7-8 (emphasis added).

itself implicates concerns MIWG has previously raised,[54] fails to establish that SIUU communications can be evidence of intended use where they are truthful, non-misleading, factual, and unbiased. As noted above, the Revised Draft itself recognizes that such communications are "scientific" in nature—*not* promotional.[55]

In addition, the Revised Draft's attempt to dictate what studies and analyses may be considered "scientifically sound" and "clinically relevant" by practicing HCPs, and thereby appropriate to serve as the basis for an SIUU communication,[56] is especially problematic considering all the foregoing. Where an SIUU communication is truthful, non-misleading, factual, and unbiased, including because it provides all information necessary for HCPs to assess the information for themselves, there would be no basis for FDA to assert that the communication may be regarded as labeling, advertising, or evidence of intended use simply because the underlying studies or analyses do not satisfy FDA's highly restrictive views of those concepts.

C. The Revised Draft raises serious First and Fifth Amendment concerns.

FDA's ability to regulate in this area is limited not only by the FDCA as described above, but also by the Constitution. MIWG has previously articulated the basic constitutional principles that are applicable here, and they merit emphasis again.

As a starting point, the First Amendment protects truthful, non-misleading communications by research and development firms, including scientific and commercial communications[57] about products and uses of those products, regardless of FDA authorization.[58] Any government restrictions on those communications are accordingly subject to "heightened scrutiny" under the First Amendment.[59] Further, laws and regulations restricting protected speech because of the identity of the speaker and "the topic discussed or the idea or message expressed" must be narrowly tailored in order to comply with the First Amendment.[60] This applies here because firms are the only stakeholders in the health care delivery system subjected to the Revised Draft, and the restrictions target the specific topic of scientific information on unapproved uses of approved medical products.

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[54] *See, e.g.*, MIWG Comments, Regulations Regarding "Intended Uses," Docket No. FDA-2015-N-2002 (Oct. 23, 2020).

[55] *See supra* notes 46 and 52 and accompanying text.

[56] *See supra* section II.A.2.

[57] *See, e.g.*, *Miller v. California*, 413 U.S. 15, 34 (1973) (The First Amendment protects speech that has "serious ... scientific value."); *Edenfield v. Fane*, 507 U.S. 761, 767 (1993) ("The commercial marketplace, like other spheres of our social and cultural life, provides a forum where ideas and information flourish.").

[58] *See Sorrell v. IMS Health Inc.*, 564 U.S. 552 (2011).

[59] *Id.* at 563-66.

[60] *Reed v. Town of Gilbert*, 576 U.S. 155, 163 (2015). In *Barr v. Am. Ass'n of Pol. Consultants, Inc.*, five justices concluded that a commercial speech restriction violated the First Amendment because it was content-based and failed strict scrutiny. 140 S. Ct. 2335, 2347 (2020) (plurality opinion); *id*. at 2364 (concurring opinion of Justice Gorsuch).

Beyond these basic points, several additional constitutional principles are particularly important here:

- *The First Amendment favors more speech, rather than less.* Methods that restrict less speech, such as disclosure requirements, are thus favored over categorical bans on speech.[61] Outright bans on speech are disfavored because they often arise from a "paternalistic assumption" that the listener will be unable to understand or utilize the information appropriately.[62] Broad prohibitions on speech are especially problematic when the underlying conduct is entirely lawful, like the unapproved use of drugs and devices that is involved here.[63]
- *Scientific speech is entitled to robust protection under foundational First Amendment principles,*[64] *including where it involves early phases of scientific and medical research.*[65]
- *Restrictions on speech must take into account not only the rights of the speaker but also the rights of listeners to receive information.* These interests are particularly important "in the fields of medicine and public health, where information can save lives,"[66] and are paramount where, as here, the recipients of the information are directly engaged in providing health care to patients, and limitations on communication of this information by research and development firms significantly impair HCPs' ability to obtain it.[67]
- *The Fifth Amendment requires restrictions on such communications to provide sufficient clarity to "give fair notice of conduct that is forbidden or required."*[68] "When speech is involved, rigorous adherence to those requirements is necessary to ensure that ambiguity does not chill protected speech."[69]

The Revised Draft runs afoul of these constitutional protections in multiple respects, as explained in more detail below. FDA should correct these constitutional deficiencies in another revised draft of the guidance.

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[61] *E.g.*, *44 Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 496-97 (1996); *Zauderer v. Off. of Disciplinary Couns. of the Sup. Ct. of Ohio*, 471 U.S. 636, 651 n.14 (1985) ("all our discussions of restraints on commercial speech have recommended disclosure requirements as one of the acceptable less restrictive alternatives to actual suppression of speech").

[62] *44 Liquormart, Inc.*, 517 U.S. at 496-97; *see also Rubin v. Coors Brewing Co.*, 514 U.S. 476, 497 (1995) (Stevens, J., concurring); *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 374 (2002).

[63] *See, e.g.*, *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012).

[64] *Bd. of Trs. v. Sullivan*, 773 F. Supp. 472, 474 (D.D.C. 1991) ("the First Amendment protects scientific expression and debate just as it protects political and artistic expression"); *Miller*, 413 U.S. at 34.

[65] *See infra* note 73 and accompanying text.

[66] *Sorrell*, 564 U.S. at 566.

[67] *See supra* notes 18-19 and accompanying text.

[68] *F.C.C. v. Fox Television Stations, Inc.*, 567 U.S. 239, 253 (2012).

[69] *Id.* at 253-54.

1. FDA's attempt to define the studies and analyses that practicing HCPs may find "scientifically sound" and "clinically relevant" imposes restrictions on a significant amount of constitutionally protected speech without sufficient justification.

The Revised Draft imposes restrictions on a significant amount of truthful, non-misleading SIUU communication. As discussed in detail above, the "scientifically sound" and "clinically relevant" concepts lack clarity and appear to exclude communication of a significant amount of SIUU, including most, if not all, SIUU based on non-RCT and "early stage" studies.[70]

This is not only practically concerning from a public and individual health perspective and contrary to statutory limitations on FDA's authority, as described above[71]; it also runs afoul of the foundational First Amendment principle that scientific speech is entitled to robust constitutional protection,[72] which applies even where medical or scientific research is at an early stage. Medicine, like other fields of scientific endeavor, requires free interchange among multiple viewpoints over time, and "open debate is an essential part of both legal and scientific analyses.... Scientific conclusions are subject to perpetual revision.... The scientific project is advanced by broad and wide-ranging consideration of a multitude of hypotheses, for those that are incorrect will eventually be shown to be so, and that in itself is an advance."[73] Given that science is inherently an iterative process, First Amendment protection is crucial even where the study or analysis that is the basis for SIUU is from an "early stage" or does not rise to the level of a determinative RCT. As noted above, this may include situations involving diseases where there is the most unmet need.[74]

The Revised Draft's restrictions are especially problematic because they implicate not only the rights of research and development firms as the source of the communication, but also the rights of HCPs as listeners.[75] The restrictions here limit HCPs' ability to obtain information that may be important to them and their patients,[76] inhibit their ability to engage in a robust dialogue and contribute to scientific innovation,[77] and undermine their interests in evaluating scientific information and deciding for *themselves* as medical practitioners whether such information should inform clinical practice decisions or serve other important public and individual health interests.[78]

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[70] *See supra* notes 29-33 and accompanying text.

[71] *See supra* section II.A.2 and text accompanying note 56.

[72] *See supra* note 64 and accompanying text.

[73] *Daubert v. Merrell Dow Pharms., Inc*., 509 U.S. 579, 596-97 (1993).

[74] *See supra* note 42 and accompanying text.

[75] *See supra* notes 66-67 and accompanying text.

[76] *See supra* notes 18-19 and accompanying text.

[77] *See supra* notes 25-26 and accompanying text.

[78] *See supra* section II.A.2.

Considering all this, neither the general discussion of public health interests and First Amendment considerations in FDA's 2017 memorandum[79] nor the Revised Draft itself establish that the specific restrictions at issue here are justified.

Indeed, the Revised Draft explicitly seeks to justify the proposed restrictions based on the improperly paternalistic assumption that HCPs may fail to appropriately determine whether SIUU is appropriate to inform a clinical practice decision, even when the information is presented in a truthful and non-misleading manner. It states: "patient harm could result from communicating information about unapproved uses of approved/cleared medical products to HCPs who are engaged in prescribing or administering those medical products to an individual patient if that information is ... not based on studies and analyses that are scientifically sound and able to provide clinically relevant information," according to FDA's highly restrictive view of those concepts.[80] The Revised Draft further posits that this is the case even if the information reflects the output of robust review by experts with relevant scientific expertise and processes accounting for conflicts of interests[81] and, in FDA's own words, is "truthful, non-misleading, factual, and unbiased and include[s] all information necessary for HCPs to interpret the strengths and weaknesses and validity and utility of the information about the unapproved use."[82]

In other words, the Revised Draft's approach is explicitly premised on the idea that HCPs may fail to appropriately assess the validity and utility of SIUU communicated to them, even when given all the information they need to do so. This is impermissibly paternalistic and overly restrictive of scientific speech,[83] even where that speech reflects the early phases of scientific and medical research.[84]

In addition, relevant experts have made clear and even FDA itself has previously recognized that a wide range of studies and analyses can serve an interest in SIUU to inform clinical practice decisions and promote other applicable interests, beyond those that might meet requirements for medical product authorization.[85] FDA has also acknowledged that the determination of whether information is "scientifically sound" and "clinically relevant" *can and should* be made by HCPs.[86] A less restrictive alternative is thus plainly available—allowing SIUU communications with appropriate context to enable HCPs to assess scientific validity and utility for themselves, including material aspects of study design, methodology, and results, as well as any material limitations related to those aspects.[87]

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[79] *See 2017 Memorandum*, *supra* note 25.

[80] Revised Draft at 9.

[81] *See supra* note 13 and accompanying text.

[82] *See, e.g.*, Revised Draft at 8-9.

[83] *See supra* notes 61-63 and accompanying text.

[84] *See supra* notes 64 and 73 and accompanying text.

[85] *See supra* notes 34-43 and accompanying text.

[86] *See supra* notes 27-28 and accompanying text.

[87] *See supra* notes 61-63 and accompanying text.

2. Additional aspects of the Revised Draft raise constitutional concerns, including a lack of required clarity that impermissibly chills protected speech.

Multiple aspects of the Revised Draft rely on vague or ambiguous standards or recommendations that do not differentiate clearly between permissible and impermissible speech, or that are unduly onerous. These ambiguities and burdens will improperly chill and restrict protected speech, in violation of the First and Fifth Amendments.

a. "Standing Alone" Limitation to Enforcement Policy

The overall lack of jurisdictional and definitional clarity described above[88] raises additional concerns when viewed in conjunction with FDA's policy regarding "intended use." Specifically, the Revised Draft asserts that FDA does not intend to use communications consistent with the guidance "standing alone" as evidence of a new intended use.[89]

The addition of the phrase "standing alone," which did not appear in the 2014 revised draft guidance, is a hefty caveat, apparently intended to preserve the government's ability to consider communications that fully satisfy the recommendations in the document as evidence of a new intended use whenever there is other evidence that the government considers relevant to that new use. Given that FDA asserts broad authority to consider "any relevant source" of evidence when determining intended use and has not clearly articulated when safe-harbored speech about unapproved uses (including certain forms of scientific exchange) may be relevant to an intended use determination,[90] firms are left in a position where even perfect adherence to the Revised Draft would not protect them from an enforcement action.

This uncertainty will no doubt chill these firms from engaging in the very scientific communications that the Revised Draft purports to allow.

b. New Disclosure Recommendations

The Revised Draft includes new recommendations for disclosures in SIUU communications, some of which are unduly onerous or vague.

As a threshold matter, there is no reason why disclosures associated with dissemination of reprints and clinical reference resources, on their own, should be any more onerous than what was described under the prior versions of the guidance. In particular, the 2014 revised draft guidance recommended that scientific articles be disseminated together with the FDA-approved labeling.[91] The Revised Draft recommends including not only a copy of the FDA-approved labeling but also separate statements reiterating specific items that are already in the

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[88] *See supra* section II.B.

[89] Revised Draft at 3 n.5.

[90] *See id.* at 7. Also, in the 2021 preamble to the final intended use rule, FDA suggests that various forms of communications about unapproved uses—including "safe-harbored" communications—would be relevant to an intended-use inquiry, even if not "determinative" of intended use when standing alone. 86 Fed. Reg. 41,383, 41,396-97 (Aug. 2, 2021).

[91] *2014 Revised Draft Guidance*, *supra* note 11, at 8.

accompanying labeling.[92] It is not clear why the prior disclosure recommendations were inadequate, and they should not be supplanted without sufficient justification.[93]

In addition, the Revised Draft suggests that the important contextual information to be included in SIUU communications should be presented in cookie-cutter, disclaimer-type format, comprising a list of specific statements.[94] This is unduly burdensome and contrary to the fundamentally scientific nature of the communications at issue here, which may be most useful to HCPs when all the relevant contextual information is provided in an integrated fashion.

Finally, the Revised Draft includes a vague and overbroad recommendation that SIUU communications include a description of any conclusions from other relevant studies that are "contrary to or cast doubt on the results shared."[95] The phrase "cast doubt on" should be revised and clarified for several reasons. For example, it may or may not include any and all studies that did not replicate the findings of the subject study despite having a different objective, study design, or methodology. This could even include RWE studies that provide relevant information but were poorly executed from a methodological standpoint. Indeed, the Revised Draft does not explicitly recommend that potentially contrary studies themselves be well-designed and well-conducted at all. Firms may thus have to navigate a minefield in determining what studies or data might be said to "cast doubt on" another's results.

c. "Persuasive Marketing Techniques"

The Revised Draft excludes communications that "use persuasive marketing techniques," but does not provide sufficient guidance as to what types of techniques would be implicated. The Revised Draft generally defines "persuasive marketing techniques" as techniques that "influence use of the products based on elements other than the scientific content of the communication."[96] It then gives three "examples" of such techniques—"the use of celebrity endorsements, premium offers, and gifts"[97]—but those are not typically used in connection with SIUU communications, and the Revised Draft does not limit persuasive marketing techniques to those three activities. This leaves firms with little clarity regarding what, if any, more relevant activities might be included.

The uncertainty here is exacerbated by the Revised Draft's inclusion of multiple footnotes citing a total of 24 references, including various articles, a book chapter, and an entire book, all of which appear to be relevant to what FDA might consider a persuasive marketing technique.[98] The Revised Draft nonetheless leaves it to firms to guess which activities

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[92] *See* Revised Draft at 13 (recommending separate statements disclosing (1) that the use has not been approved by FDA, (2) the FDA-approved use of the product and "any limitations of use specified in the FDA-required labeling", (3) any "limitations, restrictions, cautions, or warnings described in the FDA-required labeling", (4) any contraindications in the FDA-required labeling, and (5) certain risks that are in the FDA labeling).

[93] *See supra* note 60 and accompanying text.

[94] *See* Revised Draft at 13-14 (providing a list of several specific "statements" that should be included in all SIUU communications).

[95] *Id.* at 14.

[96] *Id.* at 15.

[97] *Id.* at 16.

[98] *Id.* at 15-17.

mentioned in the many hundreds of pages of cited text the Agency might deem to be problematic.

As one specific example of the uncertainty created by this approach, some of the cited texts discuss the effect simply of a firm having contact with HCPs, such as through in-person visits, mailed information, or online contact,[99] raising the question of whether mere contact with an HCP could be considered a persuasive marketing technique. If that were the case, it would effectively mean that *no* SIUU communication would qualify under the Revised Draft, as any sharing of SIUU would necessarily involve some kind of contact. Surely this cannot be FDA's intent, but the text of the Revised Draft nonetheless leaves this open to question.

As another example, the Revised Draft also states broadly that "how information is presented can impact HCP impressions of that information," citing articles discussing the effect of presenting effectiveness data in terms of relative risk rather than absolute risk.[100] This calls into question whether, among other things, a firm could ever engage in SIUU communications based on a reprint or published clinical reference resource that itself presents effectiveness data in terms of relative risk, rather than absolute risk. It is not clear whether FDA intended to exclude such communications, or how such a limitation would be justified, but again the text of the Revised Draft leaves this open to question.

The Revised Draft's creation of a broad standard, with only a few concrete but inapt examples and a plethora of cited references that seem to go well beyond the examples provided, results in significant uncertainty that should be addressed.[101]

d. Separation from "Promotional" Communications

The Revised Draft's recommendation that SIUU communications be separate and distinct from "promotional communications about approved uses"[102] creates similar vagueness concerns. FDA has never clarified when communications qualify as "promotional" as opposed to "non-promotional." Absent clear direction on the meaning of the term "separate and distinct from promotional communications," firms will be unable to determine with certainty when SIUU communications will run afoul of the guidance.

D. The Revised Draft reflects a piecemeal and incomplete approach to regulation, which raises new questions and does not promote overall clarity regarding communications by research and development firms.

MIWG is also concerned that the Revised Draft reflects FDA's continuation of a piecemeal and incomplete approach to developing policies related to communications by innovative medical product research and development firms. Rather than adopting a cohesive framework for regulation in view of public and individual health, statutory, and constitutional

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[99] *E.g.*, *id.* at 15 n.39 (citing Price SM, et al., *What Influences Healthcare Providers' Prescribing Decisions? Results from a National Survey*, Res Social Adm Pharm, 2021 Oct, 17(10):1770-79, https://pubmed.ncbi.nlm.nih.gov/33558154/).

[100] *Id.* at 16 & n.43 (citing multiple articles); *see also id.* at 15 n.39 (citing Naylor CD, et al., *Measured Enthusiasm: Does the Method of Reporting Trial Results Alter Perceptions of Therapeutic Effectiveness?*, Ann Intern Med, 1992 Dec 1, 117(11):916-21), https://pubmed.ncbi.nlm.nih.gov/1443954/).

[101] *See supra* notes 68-69 and accompanying text.

[102] Revised Draft at 17-18.

considerations, the Agency has issued various "safe harbor" policies ostensibly describing only narrow, discrete ways in which these firms may appropriately engage in non-promotional communication about unapproved uses, in some cases with many years elapsing between draft, revised, and final versions of policy, if final versions are issued at all.[103]

FDA to date has provided neither a basic accounting of all the safe harbors, nor a comprehensive explanation of how they all fit together.[104] The Revised Draft itself adds significant additional complexity and inconsistency by articulating many new concepts and standards that are not rooted in the relevant statutory or regulatory authorities and raise important new questions of interpretation and legality, as described in detail above. The accompanying *Federal Register* notice further suggests that FDA may soon add even more questions to the landscape by developing a new policy specific to communications with HCPs in their capacity as "researchers," without any explanation of why such a policy is needed.[105] The rationale for such a policy is especially unclear given the existence of a binding regulation that already permits scientific exchange[106] and the many new questions that would be posed if FDA were to impose new restrictions on communications between firms engaged in medical product research and the investigators involved in studies they sponsor.

FDA's continuation of this disjointed approach is also difficult to square with the prior FDA commitments from 2014 described above,[107] which recognized the need for FDA to provide more *overall* clarity on truthful, non-misleading scientific communications, beyond what is covered by the Revised Draft. Yet nearly a decade later, FDA has not provided any update on the status or outcome of its promised comprehensive review. Nor has FDA provided any greater clarity regarding communication of scientific information more generally.

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[103] As one example of the infirmities in FDA's approach, the Revised Draft purports to be a revision of the 2014 revised draft guidance that itself was to be a revision of the 2009 final guidance. The Revised Draft, like the 2014 revised draft guidance before it, states that it "will represent" the FDA's current thinking "when finalized." Revised Draft at 1. In contrast, the 2009 final guidance, which has technically never been withdrawn or superseded, states on its face that it reflects the FDA's "current thinking." *2009 Final Guidance*, *supra* note 11, at 1. Yet the 2009 final guidance has been removed from FDA's website, and FDA appears to be acting as if the Revised Draft reflects the Agency's current policy.

[104] Indeed, to the contrary, FDA has recently *withdrawn* draft guidance on at least one safe harbor for non-substantive reasons, and issued statements that allude to some, but not all, of the various safe harbor policies that have been articulated in various ways over the past several decades. *See, e.g.*, 80 Fed. Reg. 26,059 (May 6, 2015) (announcing withdrawal of draft guidance on "disease awareness" communications, along with 46 other draft guidance documents that were "published before December 31, 2013, and have never been finalized," in order to "improve the efficiency and transparency of the guidance development process"); 86 Fed. Reg. at 41,393 (referring to "FDA[] policies and practices, as articulated in various guidance documents, regarding the types of firm communications that ordinarily would not, on their own," establish a new "intended use," but neither comprehensively identifying those policies and practices nor acknowledging policies and practices articulated in other forms, including *Federal Register* notices that constitute binding advisory opinions under 21 C.F.R. § 10.85).

[105] 88 Fed. Reg. at 73033; Revised Draft at 6 n.11.

[106] 21 C.F.R. § 312.7(a).

[107] *See supra* notes 3-4 and accompanying text.

III. EXAMPLES OF SPECIFIC ISSUES THAT SHOULD BE ADDRESSED IN A NEW DRAFT VERSION OF THE GUIDANCE

Below we highlight specific issues with the Revised Draft that should be addressed, focusing on concepts and language that present the most important public and individual health, statutory, or constitutional concerns, as well as those that present substantial operational challenges to regulated industry. This is not an exhaustive list of revisions that MIWG believes are required.

Given the significance of the issues raised by the Revised Draft, the complex history surrounding these issues, and the numerous aspects of the Revised Draft that require clarification or revision, MIWG urges FDA to provide a new comment period after any responsive revisions and before issuing a final guidance document.[108] A new comment period would in any event be required if FDA makes any changes for which the Revised Draft did not provide adequate notice.[109]

- **The guidance should explicitly acknowledge the full spectrum of public and individual health interests promoted by SIUU communications, in addition to an interest in SIUU to inform clinical practice decisions.**

These include, as FDA has previously recognized, the general importance of sharing information about unapproved uses and an interest in furthering scientific understanding and research.[110] Encouraging robust discussion between HCPs and firms engaged in such research is also important. The guidance should be revised to reflect this.

Consistent with this, the guidance should be further revised to recognize that relevant studies and analyses need not always be "scientifically sound" and "clinically relevant," even though those concepts are relevant when there is an interest in SIUU to inform clinical practice decisions.[111]

- **Where there is an interest in SIUU to inform clinical practice decisions, the guidance should reflect FDA's own recognition that HCPs should determine for themselves when studies or analyses are "scientifically sound" and "clinically relevant," and may do so for a wide range of studies and analyses.**

Instead of recommending that SIUU be communicated only where the underlying studies or analyses meet FDA's own restrictive view of what is "scientifically sound" and "clinically relevant," the guidance should be focused only on recommending that a SIUU communication be truthful and non-misleading, including because it is accompanied by contextual information and appropriate disclosures so that HCPs are equipped to assess scientific soundness and determine clinical relevance for themselves. This should involve disclosure of any material

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[108] *See* 21 C.F.R. § 10.115(g)(1)(v) ("After providing an opportunity for comment, FDA may decide that it should issue another draft of the guidance document.").

[109] *See, e.g.*, *CSX Transp., Inc. v. Surface Transp. Bd.*, 584 F.3d 1076, 1082 (D.C. Cir. 2009).

[110] *See supra* section II.A.1.

[111] *See supra* section II.A.2.

aspects of study design, methodology, and results, as well as any material limitations related to those aspects.[112]

At minimum, FDA should revise the guidance to reflect that a wide variety of studies and analyses may be "scientifically sound" and "clinically relevant," depending on the circumstances.[113]

- **The guidance should clarify the regulatory status of SIUU communications.**

The guidance should explicitly recognize that SIUU communications do not constitute labeling, advertising, or evidence of "intended use," and are therefore not subject to FDA regulation.[114]

- **The recommendations regarding disclosures to be included as part of SIUU communications should be revised.**

The recommended disclosures associated with dissemination of reprints and clinical reference resources, on their own, without an accompanying firm-generated presentation, should not be any more onerous than what was provided under the prior versions of the guidance.[115]

In addition, the recommendations regarding specific types of contextual information to be included in SIUU communications should be re-worded to allow flexibility in how the information is provided, rather than suggesting that firms provide a formulaic list of disclosures.[116]

Finally, the guidance should provide more detail about situations where there should be disclosure about information that may "cast doubt" on the underlying studies or analyses for SIUU being communicated.[117]

- **The guidance should more clearly define what "persuasive marketing techniques" should be avoided.**

With respect to "persuasive marketing techniques," the guidance should be revised to more clearly describe the universe of relevant activities that would be implicated, without extraneous text and references suggesting that others might or might not be included. This should specifically include deleting the string of references cited in footnotes 39 and 41 to 44.[118]

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[112] *See supra* sections II.A.2, II.B, II.C.1.

[113] *See supra* section II.A.2.

[114] *See supra* section II.B.

[115] *See supra* notes 91-93 and accompanying text.

[116] *See supra* note 94 and accompanying text.

[117] *See supra* note 95 and accompanying text.

[118] *See supra* section II.C.2.c.

- **SIUU communications should include firm-generated presentations of scientific information from all types of published materials described in the Revised Draft.**

MIWG appreciates that the Revised Draft explicitly states that companies may disseminate a firm-generated presentation of scientific information "from an accompanying published reprint."[119] It is not clear, however, why this should be permitted only for reprints, and not the published clinical reference resources that are also within the scope of the Revised Draft—*i.e.*, CPGs, reference texts, and materials from independent clinical practice resources. All these materials are similarly subject to robust review by experts with relevant scientific expertise,[120] so all should qualify for similar treatment. Accordingly, the guidance should be revised to state that companies may disseminate a firm-generated presentation of scientific information "from an accompanying published reprint or accompanying published clinical reference resource."

- **The guidance should explicitly address how FDA's policy for SIUU communications relates to other relevant policies.**

The Revised Draft applies to communications of scientific information on "unapproved uses" of approved/cleared medical products,[121] where the term "unapproved use" is defined to mean: "a use that is not lawfully included as an indication or use in the FDA-required labeling of an approved/cleared medical product."[122]

This formulation is different from other FDA policies that address the distinction between information about "approved" uses and "unapproved" uses, such as the guidance on communications "consistent with" FDA-required labeling ("CFL").[123] That guidance states, for example, that information about an "unapproved use" is information that is "*not* consistent with the FDA-approved labeling," and includes an explicit reference to the 2014 revised draft guidance.

To account for this, and to make universally clear how the various policies relate, FDA should revise the SIUU guidance to explicitly state that information considered consistent with FDA-required labeling under the CFL guidance is *not* information about an "unapproved use."

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[119] *E.g.,* Revised Draft at 1, 25-26.

[120] *See supra* note 13 and accompanying text.

[121] *See, e.g.*, Revised Draft at 1.

[122] *Id.* at 5.

[123] *Guidance for Industry: Medical Product Communications That Are Consistent with the FDA-Required Labeling–Questions and Answers* (June 2018), https://www.fda.gov/media/102575/download.

CONCLUSION

MIWG is strongly committed to responsibly sharing scientific information on unapproved uses for the benefit of HCPs and the patients in their care, including for the advancement of innovative research and medical science. While we appreciate FDA's renewed efforts to develop guidance in this area, significant public and individual health interests, as well as statutory and constitutional considerations, point toward a different solution than what is posited by the Revised Draft. Accordingly, MIWG requests that FDA make significant changes as described above.

We also request that any further efforts by FDA to address communications by research and development firms do so in a more holistic, standards-based manner. The current approach of issuing detailed, highly specific guidance on a topic-by-topic basis, often with many years between issuance of draft and final versions, leaves industry in a constant state of having outdated and incomplete guidance and does not promote overall clarity in the regulatory landscape.

Respectfully submitted,

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