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By Electronic Submission

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. FDA-2008-D-0053, Communications from Firms to Health Care Providers Regarding Scientific Information on Unapproved Uses of Approved/Cleared Medical Products

To Whom It Concerns:

Washington Legal Foundation submits this response to the Food and Drug Administration's invitation for comments on its revised draft guidance on the dissemination of published materials related to off-label uses of medical products.

Founded in 1977, WLF is a public-interest law firm and policy center with supporters nationwide. WLF often appears before federal courts and administrative agencies to promote free enterprise, individual liberty, limited government, and the rule of law. To that end, WLF routinely defends commercial speech rights by appearing as an amicus curiae in state and federal courts in important First Amendment cases.[1]

WLF has also litigated in favor of First Amendment limits on the FDA's authority to restrict truthful manufacturer speech.[2] Because of that litigation, the FDA was enjoined from restricting manufacturers' ability to share peer-reviewed

[1] *See, e.g.*, *Merck & Co. v. U.S. Dep't of Health & Human Servs.*, 962 F.3d 531 (D.C. Cir. 2020); *Sorrell v. IMS Health, Inc.*, 564 U.S. 552 (2011); *R.J. Reynolds Tobacco Co. v. FDA*, 696 F.3d 1205 (D.C. Cir. 2012).

[2] *See Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51 (D.D.C. 1998), *vacated in part on other grounds*, 202 F.3d 331 (D.C. Cir. 2000).

medical texts and journal articles about off-label uses of their FDA-approved products.

As the U.S. Supreme Court has recognized, the need to ensure the free flow of truthful information "has great relevance in the fields of medicine and public health, where information can save lives."[3] Although it appropriately allows new forms of non-promotional communication—such as firm-generated presentations and clinical practice resources—the revised draft is overbroad, ambiguous, and too restrictive.

By chilling truthful, non-misleading scientific speech, the FDA's revised draft not only threatens to undermine public health, but it also disregards the Constitution. If challenged in federal court, the FDA would need to show that it has a compelling governmental interest in suppressing genuine scientific speech. The FDA cannot possibly satisfy that test.

The revised draft also ignores the unreasonable burdens it imposes on countless drug and device manufacturers, who too often face ambiguity in statutory, regulatory, and contractual obligations, and who must therefore rely on FDA's guidance to ensure that their actions are lawful.

A. Dissemination of scientific speech is fully protected by the First Amendment.

Scientific discovery is both cumulative and self-correcting. Science 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."[4] This "constant process of questioning, testing, updating, and sometimes replacing received wisdom is the hallmark of good science."[5]

No surprise, then, that scientific speech "reside[s] at the core of the First Amendment."[6] Under the Constitution's free-speech guarantee, "there is no such thing as a false idea."[7] The First Amendment "protects scientific expression and debate just as it protects political and artistic expression."[8] Like other scientific fields,

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[3] *IMS Health, Inc.*, 564 U.S. at 566.

[4] *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 597 (1993).

[5] Eugene Volokh, *In Defense of the Marketplace of Ideas*, 97 Va. L. Rev. 595, 597 (2011).

[6] *Friedman*, 13 F. Supp. 2d at 62.

[7] *Gertz v. Robert Welch, Inc.*, 418 U.S. 323, 339–40 (1974).

[8] *Bd. of Trustees v. Sullivan*, 773 F. Supp. 472, 474 (D.D.C. 1991).

medicine requires a robust exchange of views and research findings over time.[9] Because scientific debate in medicine is of great public importance, it "occupies the highest rung of the hierarchy of First Amendment values."[10]

"Choosing what treatments are or are not appropriate for a particular condition is at the heart of the practice of medicine."[11] Given the realities of clinical practice, physicians often "must make decisions in the face of uncertainty and without . . . [the] luxury of awaiting further information."[12] In each case, then, physicians must rely on their own training, experience, and judgment given each patient's unique medical history.

Ultimately "it is the physician's role to consider multiple factors, including a drug's [or device's] FDA approval status, to determine the best course of action for her patient."[13] While a product's FDA-approved label is a reliable source of information, physicians know that labeling does not always contain the most complete, or even the most accurate information. "Advances in medical knowledge and practice inevitably precede labeling revision by the manufacturer and formal [action] by the [FDA]."[14]

That is why, for instance, courts have construed the Food, Drug, and Cosmetic Act's adulteration and misbranding provisions not to prohibit "the simple promotion of a drug's off-label use because such a construction would raise First Amendment concerns."[15] Thus, the general rule for manufacturer speech aimed at healthcare providers (HCPs) is that "the speaker and the audience, not the government, assess the value of the information presented."[16] Governmental attempts at restricting

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[9] *Reilly v. Pinkus*, 338 U.S. 269, 274 (1949) ("[I]n the science of medicine, as in other sciences, experimentation is the spur of progress.").

[10] *Dun & Bradstreet, Inc. v. Greenmoss Builders, Inc.*, 472 U.S. 749, 759 (1985).

[11] *Judge Rotenberg Educ. Ctr. v. FDA*, 3 F.4th 390, 400 (D.C. Cir. 2021).

[12] Lars Noah, *Medicine's Epistemology: Mapping the Haphazard Diffusion of Knowledge in the Biomedical Community* 44 Ariz. L. Rev. 373, 382 (2002).

[13] *United States v. Caronia*, 703 F.3d 149, 167 (2d Cir. 2012).

[14] 40 Fed. Reg. 15,392, 15,394 (Apr. 7, 1975).

[15] *Caronia*, 703 F.3d at 160; *see also Amarin Pharma, Inc. v. FDA* 119 F. Supp. 3d 196, 201–02 (S.D.N.Y. 2015) (emphasizing the "therapeutic—indeed, sometimes life-saving—value of off-label uses").

[16] *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 367 (2002).

scientific speech, even speech that is "potentially misleading," warrant exacting First Amendment scrutiny.[17]

B. The revised draft threatens to chill manufacturers from communicating truthful scientific information to HCPs, in violation of the First Amendment.

Because unapproved uses may sometimes constitute the standard of care, sharing information about unapproved uses advances public health. Although it permits new forms of non-promotional communication, such as firm-generated presentations and clinical practice resources, the revised draft continues the FDA's flagrant disregard for drug and device manufacturers' free speech rights.

The revised draft explains that scientific reprints that focus on nonclinical studies or analyses alone would not be "clinically relevant" and thus inconsistent with the draft guidance. This departs from prior FDA guidance, which has conceded that articles describing significant non-clinical research of a medical device would be consistent with the guidance. Medical literature often contains preliminary observations, tentative conclusions, retractions, corrections, and reversals. All this enables physicians and other HCPs to make better informed treatment decisions for their patients. Yet the revised draft assumes, without explanation, that early-stage clinical data is unlikely to be clinically relevant. For fast-moving fields like oncology and pediatrics, HCPs must have access not only to information that has achieved broad scientific consensus, but also to reasonably debatable scientific claims that might even fall outside the mainstream. The government has no legitimate—much less compelling—interest in suppressing such information.[18]

Nor does the revised draft explain why "clinical relevance" is an appropriate *constitutional* consideration when burdening or restricting otherwise valid scientific speech. The First Amendment does not contain the words "clinically relevant," and nothing in First Amendment case law limits who may receive truthful information based on the role the government thinks they should play. Is FDA suggesting that the only permissible rationale for sharing scientific information about unapproved uses is to influence clinical practice? The FDA should explicitly answer this question in its final revised guidance.

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[17] *IMS Health*, 564 U.S. at 571 ("[I]t is all but dispositive to conclude that a law is content based and, in practice, viewpoint discriminatory.")

[18] *See generally*, Coleen Klasmeier, *FDA, Medical Communications, and Intended Use—A New Challenge to First and Fifth Amendment Constraints on Government Power*, 78 Food & Drug L. J. 2, 263–316 (2023).

Many scientific claims are not falsifiable. "[T]here are no certainties in science."[19] When a statement conveys a subjective opinion or an interpretation of data rather than an empirically falsifiable fact, "[t]here is no exact standard of absolute truth by which to prove the assertion false."[20] Because such matters are "a fruitful source of difference of opinion, even though the great majority may be of one way of thinking, the efficacy of any special method is certainly not a matter for" the government to regulate.[21]

"Medical researchers may well differ over the adequacy of given testing procedures and in the interpretation of test results."[22] Still, under the First Amendment, if a "speaker is expressing a subjective view, an interpretation, a theory, conjecture, or surmise, rather than claiming to be in possession of objectively verifiable facts, the statement is not actionable."[23] Courts have been especially leery of government efforts to punish scientific speech describing the "effectiveness of [a] particular method of treatment of disease."[24] And courts have long rejected as "almost frivolous" the suggestion that scientific claims are "inherently misleading" unless they enjoy "significant scientific agreement."[25]

To be sure, fabricating data or outright lying about objectively verifiable facts is always actionable as fraud. No reasonable scientist or manufacturer would defend such claims; they are not capable of good-faith debate. But interpretations of data that can be fairly debated by reasonable scientific minds are different. The First Amendment precludes the chilling of such scientific discourse.

The revised draft also presumes that the use of "persuasive marketing techniques" manifests an "improper intent" to market products for unapproved uses. Yet persuasiveness in commercial speech is no crime. Indeed, it makes no *constitutional* difference whether scientific speech is mixed with commercial speech to warrant First Amendment protection. Just as a newspaper does not lose its First Amendment value because it is sold for profit,[26] neither do *The Lancet* or *The New*

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[19] *Daubert*, 509 U.S. at 590.

[20] *Am. Sch. of Magnetic Healing v. McAnnulty*, 187 U.S. 94, 104 (1902).

[21] *Id*. at 105.

[22] *In re Medimmune, Inc. Sec. Litig.*, 873 F.Supp. 953, 966 (D. Md. 1995).

[23] *Haynes v. Alfred A. Knopf, Inc.*, 8 F.3d 1222, 1227 (7th Cir. 1993).

[24] *McAnnulty*, 187 U.S. at 105; see also *Reilly*, 338 U.S. at 274 (endorsing "the *McAnnulty* decision as a wholesome limitation . . . when the charges concern medical practices in fields where knowledge has not yet been crystalized in the crucible of experience").

[25] *Pearson v. Shalala*, 164 F.3d 650, 655 (D.C. Cir. 1999).

[26] *New York Times v. Sullivan*, 376 U.S. 254, 266 (1964).

England Journal of Medicine lose theirs. Such speech does not "retain[] its commercial character when it is inextricably intertwined with otherwise fully protected speech"; it remains "fully protected expression."[27]

To avoid "intrud[ing] on First Amendment values," and because "courts are ill-equipped to undertake to referee such controversies," statements "about contested and contestable scientific hypotheses" are best viewed as statements of opinion for "purposes of the First Amendment."[28] Consistent with these principles, the government generally may not condemn reasonably debatable scientific claims about the safety or effectiveness of a medical product.[29] The revised draft disregards these basic tenets of First Amendment law.

C. The revised draft fails to provide manufacturers with fair notice of what conduct violates the law.

"A fundamental principle in our legal system is that laws which regulate persons or entities must give fair notice of conduct that is forbidden or required."[30] Under the Fifth Amendment, this fair-notice requirement is now "thoroughly incorporated into administrative law."[31]

To determine "whether a party received fair notice" of what a regulatory standard requires, "courts frequently look to the regulations and other agency guidance."[32] The key question is whether "'by reviewing the regulations, a regulated party acting in good faith would be able to identify, with ascertainable certainty, the standards with which the agency expects parties to conform.'"[33]

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[27] *Riley v. Nat'l Fed'n of the Blind of N.C., Inc.*, 487 U.S. 781, 796 (1988); *see also IMS Health*, 564 U.S. at 557 ("Speech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment.").

[28] *ONY*, 720 F.3d at 496–97.

[29] *Friedman*, 13 F. Supp. 2d at 67.

[30] *FCC v. Fox Television Stations, Inc.*, 567 U.S. 239, (2012).

[31] *Gen. Elec. Co. v. EPA*, 53 F.3d 1324, 1328–29 (D.C. Cir. 1995); *Wis. Res. Protection Council v. Flambeau Min.* Co., 727 F.3d 700, 708 (7th Cir. 2013) (holding that where a "regulation is not sufficiently clear to warn a party about what is expected of it—an agency may not deprive a party of property by imposing civil or criminal liability").

[32] *Wis. Res. Protection Council*, 727 F.3d at 708.

[33] *Id.* (quoting *Howmet Corp. v. EPA*, 614 F.3d 544, 553–54 (D.C. Cir. 2010) (internal quotation marks omitted)).

The revised draft does not provide stakeholders with ascertainable certainty. In fact, a regulated company can follow every guideline FDA provides in this draft but still face an adulteration claim. The revised draft states that "FDA does not intend such [off-label] communication *standing alone* as evidence of a new intended use." So off-label communication along with other evidence *could*, in FDA's eyes, suggest a new intended use in violation of the FDCA. Regulated entities are left only to guess as to the conduct that might trigger that violation. FDA should provide them with clarity, not confusion.

The new guidance requires all non-promotional, off-label communications to HCPs to be not only "scientifically sound" but also "statistically robust." The draft guidance defines neither concept. This new, undefined standard goes beyond the "scientifically appropriate and statistically sound" standard that FDA requires for on-label promotional communications. And while FDA explores ways to separate promotional from non-promotional communications, the revised draft never defines what counts as "promotional." Again, regulated entities are left only to guess what FDA's guidance means. FDA should define "scientifically sound," "statistically robust," and "promotional" in the final revised guidance.

In another break with prior FDA guidance, the revised draft is unclear about the role that company personnel may play in communicating scientific information on unapproved uses. This lack of clarity gives FDA considerable leeway to make after-the-fact determinations that firms have engaged in improper promotional speech. It remains unknown whether FDA wants only medical personnel within companies to present off-label information, rather than sales and marketing personnel, leaving companies confused about the role of their personnel. FDA should answer this uncertainty.

Rather than provide clear guard rails and safe harbors, the FDA uses enforcement discretion as a technique for regulation, which chills the communication it should be seeking to enable—without enabling manufacturers or physicians to meaningfully challenge the guidance. The FDA must do better.

Sincerely,

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