SIDLEY

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

Re: Regulations Regarding "Intended Uses"
Docket No. FDA 2015-N-2002

The Medical Information Working Group (MIWG) submits these comments in response to FDA's proposed rule to amend the definition of intended use, 85 Fed. Reg. 59,718 (Sept. 23, 2020), currently codified at 21 C.F.R. §§ 201.128 (drugs) and 801.4 (medical devices). MIWG is a coalition of medical product manufacturers formed in 2006 to seek clarity in the FDA regulatory scheme regarding the dissemination of truthful, non-misleading information about prescription drugs, biological products, and medical devices, and to improve the regulatory and enforcement environment affecting manufacturer communications regarding those products, including products in development and new uses of marketed products.[1]

MIWG appreciates the opportunity to submit comments regarding FDA's proposed rule amending the definition of "intended use," which has been an issue of major concern to our members and the subject of ongoing engagement with the Agency. In 2013, MIWG filed a citizen petition formally requesting that FDA commence a new rulemaking proceeding to align its intended use regulations with the statutory text and the relevant case law.[2] FDA responded with a proposed rule in September 2015, on which MIWG submitted comments.[3] In January 2017, the Agency issued a final rule, which departed significantly from the proposed rule and accordingly was the subject of a Petition for Stay and for Reconsideration submitted by MIWG, along with the Pharmaceutical Research and Manufacturers of America (PhRMA) and the Biotechnology Innovation Organization (BIO), on the grounds that the final rule violated the Administrative Procedure Act, exceeded FDA's statutory authority, and raised significant constitutional issues.[4]

[1] The members of MIWG are: Amgen, Inc.; Bayer Healthcare Pharmaceuticals, Inc.; Boehringer Ingelheim Pharms., Inc.; Bristol-Myers Squibb Company; Eli Lilly and Company; Genentech, Inc.; GlaxoSmithKline, LLC; Johnson & Johnson; Novartis Pharmaceutical Corp.; Pfizer Inc.; and Samumed, LLC. MIWG's prior submissions to FDA are available at www.miwg.org.
[2] MIWG, Citizen Petition, Docket No. FDA-2013-P-1079, 19 (Sept. 3, 2013).
[3] MIWG, Comments on "Intended Use" Proposed Rule, Docket No. FDA-2015-N-2002 (Nov. 24, 2015).
[4] MIWG, PhRMA, & BIO, Petition to Stay and for Reconsideration, Docket No. FDA-2015-N-2002 (Feb. 8, 2017).

MIWG submitted further comments to FDA in July 2017[5] and February 2018[6] in connection with this rulemaking.

MIWG commends FDA for revisiting the 2017 final rule, and for proposing additional improvements to the "intended use" definition in the new proposed rule. In particular, our members support the Agency's proposal to remove the "totality of the evidence" standard and to explicitly recognize that knowledge of off-label use, either standing alone or in combination with safe-harbored speech, will not be regarded as evidence of a new intended use. Nevertheless, the proposed rule still exceeds the scope of the Agency's statutory authority and raises significant constitutional issues. In particular, as discussed further below, the proposed rule and extensive accompanying preamble continue to reflect a broader interpretation of "intended use" than can be supported by the statutory language, the accompanying legislative history, and the relevant case law, which collectively demonstrate that intended use is determined by promotional claims that have been made in the marketplace—and not by "any relevant source" as described in the preamble, or by "circumstances surrounding distribution" or "design or composition." Moreover, FDA's stated interest in addressing illicit products that, the Agency contends, could only be regulated appropriately for the protection of the public health according to a broad interpretation of intended use can be addressed under the claims-based approach. Finally, FDA's proposed rule, if finalized as written, would violate the First and Fifth Amendments by chilling truthful and non-misleading speech and failing to give fair notice that certain kinds of expression are forbidden.

For these reasons, MIWG asks FDA to promulgate a final rule that removes the "circumstances surrounding distribution" and "design or composition" provisions and to publish an accompanying preamble that reflects the claims-based interpretation of intended use, as required by the statute and the case law. Moreover, MIWG requests that FDA make clear, pending publication of the final rule, that the Agency will follow the claims-based approach.[7] In addition to our specific comments, MIWG also supports the comments submitted by PhRMA.

I. FDA's Proposed Definition of "Intended Use" Exceeds the Agency's Statutory Authority and Is Broader Than Necessary to Address the Agency's "Loophole" Concern.

A. FDA's proposed definition of "intended use" is beyond the agency's statutory authority because it is not tied to manufacturer claims.

The proposed rule doubles down on FDA's contention, set forth in the 2017 final rule, that the Agency may evaluate a product's intended use based on "any relevant source." In particular,

[5] MIWG, Comments on "Intended Use" Final Rule, Docket No. FDA-2015-N-2002 (July 18, 2017).

[6] MIWG, Comments on Proposed Partial Delay of Effective Date of "Intended Use" Final Rule, Docket No. FDA-2015-N-2002 (Feb. 5, 2018).

[7] Alternatively, we ask that FDA confirm, pending publication of the final rule, that the Agency considers the 2017 final rule *and accompanying preamble* to have been withdrawn. The preamble to the proposed rule states that "FDA is proposing to repeal the intended use amendments contained in the final rule issued on January 9, 2017, that never took effect, and to issue a new rule that would replace the January 2017 rule." 85 Fed. Reg. at 59,720. Under 21 C.F.R. § 10.85(d), the withdrawal of the 2017 rule should likewise withdraw the preamble to that rule. We nevertheless request that FDA release a public statement clarifying the inapplicability of the 2017 preamble, which has created significant confusion because of its breadth and inconsistency with other FDA statements and with the applicable law.

the proposed rule includes a lengthy preamble discussion advancing this broad reading of intended use, and the proposed codified language retains the existing "circumstances surrounding distribution" prong of the regulation and seeks to add an entirely new "design or composition" prong. In proposing such a broad definition of intended use, the proposed rule runs contrary to the statute, which dictates that intended use is created by promotional claims made by the manufacturer concerning the product in the marketplace.

Indeed, the preamble accompanying the proposed rule is replete with references to "types of evidence relevant to determining" intended use—as though the concept of "intended use" were properly understood as establishing an evidentiary standard governing the kinds of speech and activities that *FDA* is entitled to use in establishing that a given product has a particular intended use.[8] That is not the law. Courts have long accepted that "intended use" is *created by the manufacturer*, according to its claims for the product to prospective purchasers or users; in the language of FDA's regulations, it is an "objective" standard. The claims-based approach is the only approach that adequately accounts for the legislative history, the text and operation of the statute when read as a whole, and the case law. That is why the principle of manufacturer promotional claims as the touchstone of intended use has been accepted by the courts "as a matter of statutory interpretation."[9]

The seminal case using the "any relevant source" formulation is *United States v. 3 Cartons . . . "No. 26 Formula GM."*[10] There, the manufacturer sought to evade regulation of its product as a drug by omitting and even disclaiming therapeutic uses in the product's label. The court held that it could consider "any source which discloses the intended use," focusing on "literature" the manufacturer had used to promote its product to prospective buyers.[11] The manufacturer's literature "consistently represented these products as efficacious in the treatment, mitigation, and prevention of many ailments."[12] Thus, the court concluded that the intended use of the product

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[8] 85 Fed. Reg. at 59,719 (stating, in setting forth the purpose of the proposed rule, that "FDA is proposing to amend" the regulations "*describing the types of evidence relevant* to determining a product's intended uses" under the Agency's enabling statutes and implementing regulations (emphasis added)); *id*. at 59,721 ("FDA's longstanding position is that, in evaluating a product's intended use, any relevant source of evidence may be considered."). The types of "evidence" that FDA cites include "consumer intent," *id.* (quoting *Travia*, 180 F. Supp. 2d at 119); "overall circumstances," *id.* (quoting *United States v. Storage Spaces Designated Nos. 8 & 49*, 777 F.2d 1363, 1366 n.5 (9th Cir. 1985)); "witness testimony" and "other evidence regarding a training program and financial arrangements offered by the defendant," *id.*; "in combination with other facts, a firm's knowledge that health care providers are prescribing or using its approved or cleared medical product for an unapproved use," *id.*; communications in conjunction with "other evidence of a new intended use of a product," *id.*at 59,723 n.7; "situations where products contained a [certain] pharmacological ingredient," *id.* at 59,723; "firms' directions to their sales forces," *id.*; "[r]epresentations that the product contains a particular ingredient to imply a physiological effect," *id.* at 59,724–25; "product characteristics and design," including "known physiological effects," "known use (recreational or medical) of a product that is unapproved for any medical use," or "design or technical features," *id.* at 59,725; "circumstances surrounding the distribution of the product and the context in which it is sold," including "[t]o whom and for whom the products are offered" and "[c]ircumstances and context surrounding the sale," *id.*; "objective evidence," including "any circumstances surrounding the distribution of the product or the context in which it is sold," 82 Fed. Reg. at 2,195-96; 80 Fed. Reg. at 57,757.

[9] *Action on Smoking & Health v. Harris*, 655 F.2d 236, 239 (D.C. Cir. 1980). *See also* S. Rep. 493, 73d Cong. 2d Sess., 3 (1934); S. Rep. 361, 74th Cong. 1st Sess., 4 (1935) ("The manufacturer of the article, through his representations in connection with its sale, can determine the use to which the article is to be put.").

[10] 132 F. Supp. 569, 573 (S.D. Cal. 1952).

[11] *Id*. at 573-75.

[12] *Id*. at 573.

was established by other sources of promotional representations that the manufacturer had disseminated regarding the product, even though those uses had been disclaimed on the label.

Other cases using the "any relevant source" formulation confirm this understanding. In *V.E. Irons, Inc. v. United States*, the court explained that it could "look at all relevant sources" when the manufacturer argued that the court should confine its intended use analysis "to the labels on the drug or the 'labeling.'"[13] The court ultimately examined the firm's literature and oral statements made by an executive at a promotional lecture and by authorized sales distributors and relied on those statements in finding the firm's products were drugs.[14] The court did not state or otherwise suggest that it could find an intended use never mentioned in the manufacturer's promotional claims about its products. Similarly, in *United States v. Storage Spaces Designated Nos. 8 and 49*, the Ninth Circuit looked to promotional sources including promotional leaflets, catalogues and advertisements, and product labels—all of which included promotional claims about the product at issue.[15] The other cases cited in the preamble generally follow this same pattern.[16] Other cases, not cited in the preamble, likewise reflect the claims-based interpretation.[17]

The principle of statutory interpretation known as *ejusdem generis* further supports the same interpretation. Nearly all of the cases cited in the preamble use the phrase "any relevant source" within the broader statement, "the intended use of a product may be determined from its label, accompanying labeling, promotional material, advertising, and other relevant sources."[18] Every source specified in this list is a source of *claims* about the product. When general words like "any other relevant source" follow specific words (here, "labeling, promotional material, and advertising"), the general words embrace "only objects similar in nature to those objects enumerated by the preceding specific words."[19] Therefore, the phrase "other relevant source" must,

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[13] 244 F.2d 34, 44 (1st Cir. 1957).

[14] *Id.*

[15] 777 F.2d 1363, 1366 (9th Cir. 1985).

[16] *See, e.g.*, *United States v. Undetermined Quantities of an Article of Drug Labeled as "Exachol,"* 716 F. Supp. 787, 792 (S.D.N.Y. 1989) ("The claims clearly identify a product which is intended to prevent cholesterol deposits and thereby to mitigate the possibility of coronary thrombosis."); *United States v. LeBeau*, 2016 WL 447612 (E.D. Wisc. Feb. 3, 2016) (considering labeling and a claim that product "reduces food allergies" as determining a product's intended use); *Hanson v. United States*, 417 F. Supp. 30, 35 (D. Minn.), *aff'd*, 540 F.2d 947 (8th Cir. 1976) (examining "promotional materials" which contained drug claims).

[17] *See also Prevor v. FDA*, 67 F. Supp. 3d 125, 139 n.8 (D.D.C. 2014) ("FDA is entitled to consider Prevor's own promotional materials in determining the intended use of a product."); *United States v. Article of Drug Designed B-Complex Cholinos Capsules*, 362 F.2d 923, 925-26 (3d Cir. 1966) ("radio broadcasts" that included "advertisements . . . presented as commercials" established intended uses); *United States v. Articles of Drug…250 Jars "Cal's Tupelo Blossom U.S. Fancy Pure Honey,"* 344 F.2d 288, 289 (6th Cir. 1965) ("a reading of the booklets and mailing leaflets resulted in the inescapable conclusion that such honey was intended to be used as a drug"); *United States v. Millpax, Inc.*, 313 F.2d 152, 154-55 (7th Cir. 1963) (prior customer "testimonials" published in a magazine and an oral recommendation to a potential customer showed that a "cancer cure" was a drug notwithstanding a disclaimer sent by the defendant's attorney); *Nature Food Ctrs., Inc. v. United States*, 310 F.2d 67, 69-70 (1st Cir. 1962) ("lectures" and "notes" distributed by company representatives "made fulsome claims as to the preventative and curative qualities of [the] various products"); *United States v. Hohensee*, 243 F.2d 367, 370 (3d Cir. 1957) ("oral representations to users and prospective users" were "no less relevant" than labeling because "[b]oth show that the products shipped were to be used as drugs").

[18] *E.g.*, *United States v. Article of 216 Cartoned Bottles, "Sudden Change,"* 409 F.2d 734, 739 (2d Cir. 1969). This formulation is repeatedly used in the cases cited in the proposed rule. *See* 85 Fed. Reg. at 59,721.

[19] *Yates v. United States*, 574 U.S. 528, 545 (2015).

by operation of traditional canons of statutory construction, be interpreted to mean *promotional claims*.

Prior attempts to expand intended use beyond claims have been rejected by both FDA and the courts. In *Action on Smoking and Health v. Harris*, for example, a citizen petition asked FDA to rely on "consumer intent" to find that cigarettes were drugs under the FDCA despite the lack of therapeutic claims made for them in promotion. Both the Agency and the court rejected the request.[20] The court held that the statutory intent was that "jurisdictional analysis [under the FDCA] would focus upon the existence of *representations made by the manufacturer*."[21] The court further noted that the actual use of a product would support "no inference at all" regarding the manufacturer's intended use, "if such [product] were shipped without advertising" regarding that use.[22]

Similarly, in the 1990s, FDA reinterpreted intended use using tort and criminal law conceptions of "intent," in an attempt to regulate tobacco products.[23] This effort was roundly rejected by the courts,[24] but the proposed rule nevertheless appears to reproduce that error, repeatedly using references to a product seller's intent instead of "intended use."[25]

Likewise, the preamble's citation to *United States v. Vascular Solutions, Inc.*[26] falls short. MIWG has previously pointed out that this *in limine* district court opinion is based on a hypothetical set of facts. And the opinion is contrary to the actual facts in *United States v. Articles of Drug for Veterinary Use*, where a circuit court of appeals held that the government could *not* rely on written material stored in a warehouse to establish intended use without showing that

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[20] *See* 655 F.2d 236, 239 (D.C. Cir. 1980).

[21] *Id*. at 238.

[22] *Id*. In dicta, the court suggested the possibility of establishing intended use without promotional claims only where there was "a substantial showing" that would "justify an inference as to the vendors' intent." *Id.* Such a demonstration would require that "consumers must use the product predominantly and in fact nearly exclusively with the appropriate intent before the requisite statutory intent can be inferred." *Id.* at 240. *United States v. Travia*, which the preamble relies upon, found that "the environment" (sale of unlabeled nitrous oxide balloons in the parking lot outside of a rock concert) "provided the necessary information between buyer and seller" to establish intended use. 180 F. Supp. 2d 115, 119 (D.D.C. 2001). Under the extreme and "obviously unique" facts of the case, *id.*, the probative value of the environment was so strong as to negate any explanation other than the sellers' intended use of the balloons as drugs. This outlier case does not support FDA's broader reliance on a non-claims-based interpretation of intended use. Further, unlike both *ASH* and *Travia*, the proposed rule here incorporates no requirement that the probative value of circumstantial, non-claims-based evidence must negate any explanation other than the sellers' intended use of the product as a drug or device.

[23] *E.g.*, 61 Fed. Reg. 44,396, 44,546, 44,561-62 (Aug. 28, 1996); 61 Fed. Reg. 44,619, 44,992-94 (Aug. 28, 1996). *See also* David Kessler, A Question of Intent: A Great American Battle With A Deadly Industry 270–73 (2002) ("Traditionally, the FDA determined a company's intent from the label or the words used in advertising and elsewhere. . . . After months of effort, we felt confident that all three theories—foreseeability, actual consumer use, and explicit knowledge—provided a strong basis for declaring jurisdiction over tobacco. As sensible and straightforward as our legal analysis seemed to us, it was a pioneering interpretation of the Food, Drug, and Cosmetic Act.").

[24] *See Brown & Williamson Tobacco Corp. v. FDA*, 153 F.3d 155, 163 (4th Cir. 1998), *aff'd* 529 U.S. 120 (2000).

[25] *Compare, e.g.*, 85 Fed. Reg. 59,718, 59,725 ("a firm will not be regarded as intending an unapproved use . . ."), *with* Richard M. Cooper, *The WLF Case Thus Far: Not with a Bang but a Whimper*, 55 Food & Drug L.J. 477 (2000) ("It is not that intended uses are established by events in the minds of manufacturers (whatever those may be) and that the statements are merely evidence of what has occurred in those minds; rather, the statements create the intended uses, and the minds (and evidence of what has occurred in those minds) are irrelevant.").

[26] 181 F. Supp. 3d 342 (W.D. Tex. 2016).

similar claims had been made in marketing the product.[27] FDA's preamble did not cite this opinion, which is notable because it held that intended use is based on claims that are "promotional in nature" and "distributed in relation to the . . . products."[28]

The statutory and regulatory regime provides further support for a claims-based interpretation of intended use. When a lawfully marketed medical product is put to an unlabeled use, the statutorily prescribed consequence is a supplemental premarket submission—an sNDA, or a new 510(k), for example—*only* where the manufacturer has promoted its product for that use (in which case, the claim defines the scope of required clinical data and other substantiating information). For unlabeled uses in the absence of promotional claims, the regulatory scheme includes multiple provisions imposing regulatory duties on manufacturers. For example, a manufacturer of a drug that has a common off-label use is required to provide risk information relevant to that use in the drug's labeling.[29] Moreover, a medical product manufacturer is subject to rules requiring post-market reporting for drugs and medical devices, and these provisions apply to events occurring with both labeled and unlabeled uses.[30] Indeed, FDA cites these "obligations and responsibilities" and expressly affirms their continued force.[31] In other words, the remedy for an unclaimed use is a combination of post-market risk mitigation techniques such as the collection, review, and potential labeling description of information regarding the risks associated with that use. The remedy is not a required premarket submission, which would be the result under the proposed rule where FDA asserts a new intended use based on evidence other than claims, such as the design or composition of a product.

The claims-based approach is the *only* approach that honors Congress's intentions and avoids the array of dislocations that follow from the alternative, novel interpretations with which FDA has flirted from time to time in the past, and which the Agency is seeking to entrench with the proposed rule. Intended use dictates not only the regulatory categorization of an article—whether it is properly regulated as a drug or medical device under the FDCA—but also the nature and quantity of scientific evidence that the manufacturer must submit to FDA in substantiation of the claims that comprise those intended uses.[32] If a manufacturer were held to account for an intended use based on one of FDA's alternative theories—for example, based on the design or composition of a device—then the manufacturer would be in a Catch-22: it would have to generate new appropriate data to demonstrate the clinical utility of the product for that ostensibly "intended" use. The alternative would be to face liability under the statute for introducing or delivering for introduction into interstate commerce a misbranded medical product, in violation of a federal criminal statute.[33]

It is not an answer that, in principle, such a manufacturer could resolve the dilemma by simply generating the relevant data and preparing the required regulatory submission. It is increasingly challenging for even a sophisticated manufacturer with decades of regulatory

[27] 50 F.3d 497, 501 (8th Cir. 1995).
[28] *Id.*
[29] 21 C.F.R. § 201.56(a)(2).
[30] 21 C.F.R. § 314.80, Part 803.
[31] 85 Fed. Reg. at 59,725 n.14.
[32] *See* 21 U.S.C. §§ 355(b) (contents of a new drug application); 360e(c) (contents of a premarket approval application for a medical device); 21 C.F.R. § 807.87 (contents of a 510(k) submission).
[33] 21 U.S.C. § 331(a).

experience to conduct clinical trials and prepare regulatory submissions in pursuit of FDA marketing authorization.[34] Beyond the economic consequences of allocating capital to a new development program, entities engaged in medical product innovation must contend with the difficulty in identifying and recruiting subjects who are eligible to participate in clinical investigations.[35] This challenge is even greater with respect to rare diseases affecting extraordinarily small numbers of patients worldwide.[36] Many product developers are also subject to demands linked to funding—for example, a publicly traded company has a legal duty to deploy resources in a particular way to satisfy statutory and common-law obligations to shareholders. These responsibilities cannot be fulfilled if a manufacturer invests in resource-intensive clinical development unlinked to an economically rational outcome.

In sum, while the preamble to FDA's proposed rule asserts, based on selected judicial decisions, that "any relevant source of evidence may be considered" to determine intended use,[37] in fact the cited cases—and indeed the overall body of relevant cases—show that intended use is determined by *promotional claims*, the relevant sources of which are promotional labeling, advertising, and oral statements by sales representatives. The only interpretation of intended use that adequately accounts for these authorities, and for the statutory scheme, is the claims-based interpretation.

B. FDA's proposed non-claims-based definition of intended use is not necessary to address supposed "loopholes."

Despite the preamble's references to FDA's desire to provide manufacturers with clarity, the proposed rule appears largely driven by concern that the Agency would be unable to regulate illicit products in the absence of an aggressive reinterpretation of intended use.[38] As has been previously demonstrated, in *each and every instance* identified by FDA as requiring a non-claims-based reading of intended use, the product of concern is subject to regulatory action under other

[34] *See, e.g.*, Matthijs D. Kruizinga, et al., *The Future of Clinical Trial Design: The Transition from Hard Endpoints to Value-Based Endpoints* 375–76, in CONCEPTS & PRINCIPLES OF PHARMACOLOGY (J.E. Barrett et al., eds. 2019) (noting the "increase in the size of clinical trials and the accompanying regulation," which has "made clinical trials much more difficult and expensive to conduct").

[35] *See* FDA, Report: Complex Issues in Developing Drugs & Biological Products for Rare Diseases & Accelerating the Development of Theories for Pediatric Rare Diseases, at 14 (July 2014), https://www.fda.gov/media/89051/download. FDA's report notes, for example, that "deficiencies in the pediatric clinical research infrastructure . . . can be a key challenge to the planning of clinical trials for pediatric patients." *Id.* at 14 (citing Edward M. Connor et al., *Meeting the Demand for Pediatric Clinical Trials*, 6 SCI TRANSLATIONAL MED. ISS. 227, at 1 (Mar. 12 2014), https://stm.sciencemag.org/content/scitransmed/6/227/227fs11.full.pdf).

[36] *See id.* at 13–14 ("Developing safe and effective products to treat rare diseases can be very challenging.").

[37] 85 Fed. Reg. at 59,721.

[38] 85 Fed. Reg. at 59,723 ("Considering evidence other than express claims often ensures that FDA is able to pursue firms that attempt to evade FDA medical product regulation by avoiding making express claims about their products."). Prior agency statements have likewise emphasized the Agency's interest in assuring that it can act against products that appear to the Agency to present significant risks to users or threaten the integrity of the premarket review system for medical products. *See, e.g.*, Remarks by Lowell Schiller, JD at the Food and Drug Law Institute's Annual Conference on Medical Product Advertising and Promotion (Oct. 17, 2019), https://tinyurl.com/y4t9rqho.

provisions of federal law.[39] It is not an adequate defense of the non-claims-based approach that it simply makes it easier for FDA to act against those products.[40]

FDA can address these "loophole" products separately, without stretching the definition of intended use and the surrounding statutory scheme beyond their permissible bounds. To the extent FDA is concerned about cases that have challenged FDA's existing systems and processes because of administrative issues, the solution is programmatic alignment efforts that do not require new legal authorities.[41] FDA is also free to seek legislative changes targeted to gaps in its statutory authority, such as changes that would assure the proper regulation of putative dietary supplements containing drug active ingredients.[42]

In addition, FDA could propose an evidentiary approach to intended use, but that regime would be much more limited than the one envisioned in the proposed rule. In particular, under such a regime, in a contested proceeding in which a court or a jury is required to consider whether a product is properly subject to regulation under the drug or medical device provisions of the FDCA because of its intended use, the government could introduce evidence from a potentially wide range of sources, but only for a limited purpose. The evidence would be admissible in such a case—subject to the Federal Rules of Evidence, constitutional limitations, and any other relevant constraint—for consideration by the trier of fact only to determine *whether, in fact, a promotional claim was made*. In other words, where the government comes forward with evidence that the public "expressions" of a manufacturer or its agent arguably promote a product for a new intended use, the government would be permitted to submit evidence of, for example, the manufacturer's instructions to its sales force for the purpose of demonstrating that the public expression occurred and that it was a promotional claim.[43] In this way, FDA could establish an appropriate role for the use of a broad range of evidence in cases involving intended use issues, without exceeding the scope of the Agency's statutory authority.

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[39] *See* MIWG, Comments on "Intended Use" Final Rule, Docket No. FDA-2015-N-2002, 11-13 (July 18, 2017).

[40] *See FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 125 (2000) ("Regardless of how serious the problem an administrative agency seeks to address, however, it may not exercise its authority 'in a manner that is inconsistent with the administrative structure that Congress enacted into law.'" (quoting *ETSI Pipeline Project v. Missouri*, 484 U.S. 495, 517 (1988))).

[41] *See* FDA, Office of Regulatory Affairs, *Program Alignment & ORA*, https://www.fda.gov/about-fda/office-regulatory-affairs/program-alignment-and-ora (last updated Apr. 29, 2019) (describing program alignment as a way "to enhance" FDA's "ability to protect the public health" and to "modify certain processes with the goal of improved cross-agency communication, collaboration, and clarity").

[42] For example, the SUPPORT Act, Pub. L. No. 115-271, § 3022, 132 Stat. 3893, 3940 (2018), added Section 801(u) to the FDCA, which allows FDA to treat certain imported products as drugs when they enter the country based on what substances are in them, including when they contain active pharmaceutical ingredients of an approved drug.

[43] *See* Fed. R. Evid. 401. *United States v. Travia*, which FDA relies upon in the preamble, can be interpreted so that it is consistent with the claims-based approach. 180 F. Supp. 2d 115, 119 (D.D.C. 2001). Although the *Travia* court ostensibly relied upon the circumstances surrounding the distribution of the product in determining intended use, the court emphasized: "the sellers did not need to *label or advertise* their product, as the *environment provided the necessary information* between buyer and seller." *Id.* (emphasis added). Thus, the "environment" provided "information" that served the role of labeling or advertising under the facts of that unique case.

II. If Revised As Proposed, the Intended Use Regulations Would Continue to Raise Significant Constitutional Concerns.

A. FDA inappropriately minimizes the First and Fifth Amendment implications of the proposed rule and its potential to chill truthful, non-misleading manufacturer communications.

FDA asserts in a footnote that, "[b]ecause 'intended use' is only one element of an alleged violation of the FD&C Act, this rule does not itself implicate the First Amendment."[44] This is a remarkable statement, given that government enforcement of off-label promotion is *wholly dependent* upon how the government may establish a new intended use for an approved or cleared medical product, including the use of speech that is protected by the First Amendment. While intended use may literally only be "one element" of an alleged misbranding violation for lack of adequate directions for use,[45] it is the crucial element that implicates the First Amendment. Thus, any changes to FDA's intended use regulations need to be carefully analyzed to ensure that they comport with the First Amendment.

As MIWG has previously explained, vague or ill-defined standards for determining intended use raise significant constitutional concerns by chilling the communication of truthful, non-misleading information about medical products.[46] The First Amendment restricts the government's ability to regulate truthful, non-misleading manufacturer speech,[47] and the Fifth Amendment requires that the boundaries between permissible and impermissible communications be clearly drawn. The government must provide regulated parties with "fair notice of conduct that is forbidden or required," and this concern is heightened when a lack of clarity could chill protected speech.[48] Vague and overbroad regulation is "particularly treacherous" because the threat of criminal sanctions would deter a party "seek[ing] to exercise protected First Amendment rights."[49]

In this regard, courts have expressed frustration with the manner in which the government has historically applied the statutory and regulatory framework in off-label promotion cases, given the lack of clarity. For example, one district court in a recent case—despite upholding the defendants' misdemeanor convictions on the facts of the case—stated that FDA's "statutory and

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[44] 85 Fed. Reg. at 59,723. FDA adds in the same footnote that "this rule . . . does not attempt to resolve all First Amendment arguments that might be made by a firm in defending against an enforcement action under the FD&C Act." In a similar vein, MIWG's specific comments on the current proposed rule do not attempt to detail all possible First Amendment defenses to such an enforcement action.

[45] 21 U.S.C. § 352(f)(1).

[46] *See, e.g.*, MIWG, Comments on "Intended Use" Final Rule, Docket No. FDA-2015-N-2002, 2-7 (July 18, 2017); MIWG, PhRMA, & BIO, Petition to Stay and for Reconsideration, Docket No. FDA-2015-N-2002, 20-21 (Feb. 8, 2017); MIWG, White Paper: Systemic, Societal, and Legal Developments Require Changes to FDA's Regulation of Manufacturer Speech, Docket No. FDA-2013-P-1079-0007, 50-54 (Oct. 31, 2014); MIWG, Citizen Petition, Docket No. FDA-2013-P-1079, 15-19 (Sept. 3, 2013).

[47] *E.g.*, *United States v. Caronia*, 703 F.3d 149, 160 (2d Cir. 2012) (holding that truthful and non-misleading promotional claims are protected by the First Amendment and invoking the canon of constitutional avoidance to construe the FDCA as not criminalizing the promotion of a drug's off-label use).

[48] *FCC v. Fox Television Stations, Inc.*, 567 U.S. 239, 253-54 (2012).

[49] *Id.* at 254; *see also Keyishian v. Bd. of Regents of the U. of N.Y.*, 385 U.S. 589, 604 (1967) (noting that "'standards of permissible statutory vagueness are strict in the area of free expression . . . Because the First Amendment freedoms need breathing space to survive, government may regulate in the area only with narrow specificity'") (quoting *NAACP v. Button*, 371 U.S. 415, 438 (1963)); *Buckley v. Valeo*, 424 U.S. 1, 76-77 (1976).

regulatory scheme needs to be rethought."[50] Additionally, the Second Circuit in *United States v. Caronia* determined that the government's construction of the FDCA, which "legalizes the outcome—off-label use—but prohibits the free flow of information that would inform that outcome, . . . does not directly advance its interest either in reducing patient exposure to off-label drugs or in preserving the efficacy of the drug approval process."[51]

The public interest is aligned with the constitutional considerations because the public health is best served when decisions regarding the uses of approved or cleared medical products are informed by as much truthful and non-misleading information as possible.[52] Because manufacturers often have the earliest, surest access to new information about their products and also have the resources and infrastructure to share this information in a timely and efficient manner, they are well-positioned to provide health care professionals with accurate and up-to-date scientific and medical information. FDA has long recognized the public health importance of accurate information about off-label use.[53] The agency's prior statements have made clear that manufacturer dissemination of information about unlabeled uses of approved or cleared medical products can be necessary for the advancement of patient care and public health.[54]

FDA's proposed rule exacerbates the chill on truthful, non-misleading manufacturer communications resulting from the lack of clear rules enabling manufacturers to determine in advance whether their communications are lawful.[55] While FDA has rightly rejected the "totality of the evidence" standard,[56] the proposed rule still raises the same constitutional and public health concerns. In describing the examples-based approach in Section V, the preamble indicates that the examples "are provided for illustrative purposes only and are not intended to be comprehensive or restrictive."[57] It states further that "[i]n fulfilling its mission to protect the public health, FDA will evaluate the individual and unique circumstances of each case in determining a product's intended use."[58] FDA adds that "[i]n some cases, a single piece of evidence may be dispositive of a product's intended use," whereas "[i]n others, several elements combined may establish a product's intended use."[59] Even in purporting to provide regulatory relief by identifying instances in which an intended use will not be found, the preamble equivocates, describing "[o]ne example

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[50] *United States v. Facteau*, No. 15-cr-10076, 2020 WL 5517573, *1 (D. Mass. Sept. 14, 2020). The court explained: "Currently there is no statute that specifically prohibits off-label marketing and yet the Government continues to prosecute the conduct by patching together the misbranding and adulteration regulations, *thereby criminalizing conduct that it is not entirely clear Congress intended to criminalize*. . . . [W]here a conviction can result in exclusion from healthcare programs, likely a death knell for any company, it is also *important for the regulatory and law enforcement regime to clearly spell out what is and is not prohibited conduct*." *Id.* (emphasis added).

[51] 703 F.3d at 167.

[52] *See id.* ("[I]n the fields of medicine and public health, 'where information can save lives,' it only furthers the public interest to ensure that decisions about the use of prescription drugs, including off-label usage, are intelligent and well-informed." (quoting *Sorrell v. IMS Health Inc.*, 564 U.S. 552, 566 (2011))); 63 Fed. Reg. 64,556, 64,579 (Nov. 20, 1998) (recognizing the "public health gains associated with the earlier dissemination of objective, balanced, and accurate information on important unapproved uses of approved products").

[53] *See* MIWG, Comments on "Intended Use" Final Rule, Docket No. FDA-2015-N-2002, 4 (July 18, 2017) (summarizing prior FDA statements dating back to 1992).

[54] *See id.*

[55] *Sorrell v. IMS Health, Inc.*, 564 U.S. 552 (2011); *FCC v. Fox Television Stations, Inc.*, 567 U.S. 239, 253 (2012).

[56] *See* 85 Fed. Reg. at 59,721, 59,727.

[57] *Id.*at 59,724.

[58] *Id.*

[59] *Id.*

that would not, *standing alone*, be considered evidence of a new intended use," while indicating that that example "*might* include" the specific scenario described.[60] FDA's ad hoc, overbroad approach makes it practically impossible for manufacturers to engage in protected speech—including safe-harbored speech—without having to risk significant federal regulatory and potential criminal liability.[61]

The preamble sows further confusion in referring to FDA's "current practice" and asserting that the 2017 amendments, which introduced a "totality of the evidence" standard, "did not reflect a change in FDA's approach regarding types of evidence of intended use for drugs and devices."[62] This language mirrors a statement made by the Commissioner when FDA proposed an indefinite delay in the effective date of provisions amending the intended use regulations in 2018.[63] However, as MIWG has explained, FDA's proposals to amend §§ 201.128 and 801.4 were, in fact, a change to FDA's approach, and they remain so.[64]

FDA has previously taken positions in litigation inconsistent with the "totality" approach, further calling into question FDA's assertions with respect to "current practice." In *Allergan v. United States*, for example, the Agency explained that it ordinarily would not regard certain activities as "evidence of intended use."[65] The government's filings, including a declaration by CDER's Deputy Director for Clinical Science, noted a difference between "promotion" and "non-promotional" statements. In the government's later reply brief, it explained that promotion encompasses "prescribing," "recommending," and "suggesting" the use of a drug, while statements that do not prescribe, recommend, or suggest a use are not promotional. Indeed, the declaration stated that FDA has *never* sought to forbid manufacturers from providing warnings about off-label uses, provided that the warnings do not represent "back door" promotion, meaning that they do not explicitly or implicitly promote the efficacy of the unapproved use.[66] These and other litigating positions are cited by FDA in the proposed rule preamble, but they are not

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[60] *Id.* at 59,725 (emphasis added).

[61] By the same token, the cost-benefit analysis contained in Section VII.B of the preamble is also faulty. The preamble states that the "benefit of this proposed rule is the added clarity and certainty for firms and stakeholders regarding the evidence relevant to establishing whether a product . . . is intended for a new use." *Id.* at 59,720. However, the proposed rule will not achieve this benefit and instead will chill protected speech. By imposing an overly broad evidentiary approach to "intended use" and failing to clarify what manufacturer speech is permitted, the proposed rule will "impose costs on currently marketed products."

[62] *Id.* at 59,719.

[63] *See* 83 Fed. Reg. 2092 (Jan. 16, 2018). The Commissioner stated that, "[b]y delaying implementation of these portions of the final rule we are not creating new policy, but instead reverting to the agency's existing and longstanding regulations and interpretations on determining intended use for medical products. These are the same regulations and interpretations that have been in effect for decades." Statement from FDA Commissioner Scott Gottlieb, M.D., on FDA Decision to Seek Additional Time to Reassess Rule That Would Have Changed Longstanding Practices for How the Agency Determined the "Intended Use" of Medical Products (Jan. 12, 2018).

[64] *See, e.g.*, MIWG Comment re: Proposed Rule: Clarification of When Products Made or Derived from Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses" (Docket No. 2015-FDA-N-2002) (Nov. 24, 2015), at 3 ("[T]he proposed rule advances an interpretation of intended use that impermissibly purports to rely on evidence beyond manufacturers' promotional claims. … Courts have invoked the "other relevant source" language, which originated in [*Hanson v. United States*, 417 F. Supp. 30 (D. Minn. 1976)], exclusively in cases in which there *were* manufacturer promotional claims.").

[65] *See* Decl. of Robert Temple, *Allergan v. United States*, No. 09-cv-01879 (D.D.C. Dec. 11, 2009).

[66] *Id.* at 5; Reply in Supp. of Mot. to Dismiss and for Summ. J. and Resp. to Cross-Mot. For Summ. J. at 7-8, *Allergan v. United States*, No. 09-cv-01879 (D.D.C. Mar. 29, 2010).

supportive of FDA's broad interpretation of intended use that threatens to chill accurate manufacturer speech about off-label uses.

Because such speech is constitutionally protected and vitally important for public health reasons, FDA should assure that the final rule provides manufacturers with clear *a priori* standards distinguishing permitted from prohibited speech.

B. FDA should codify the non-binding guidance documents it relies upon as part of its defense of the proposed rule under the First Amendment.

In defending the proposed rule under the First Amendment, FDA states that the proposed revisions "do not reflect a change in FDA's policies and practices as articulated in various guidance documents, regarding the types of firm communications that ordinarily would not, on their own, establish the firm's intent that an approved or cleared medical product be used for an unapproved use."[67] FDA adds: "If a firm's communication is consistent with the recommended practices described in FDA guidance, such a communication on its own, would not be evidence of a new intended use."[68] FDA "invites comment on whether any elements of these guidances warrant codification in the regulations."[69]

As MIWG has repeatedly urged, FDA should codify in binding regulations its policies regarding manufacturer communication of scientific and medical information.[70] Regulating the dissemination of truthful, non-misleading scientific and medical information through expressly non-binding—and often draft—guidance documents raises First and Fifth Amendment concerns. Until they are codified into clear, binding rules, these "safe harbors" cannot comply with the Due Process Clause's requirement that the government create precise rules that provide regulated industries "fair notice of what is prohibited."[71]

While MIWG appreciates FDA's acknowledgement that various "safe harbors" exist, there remains a lack of clarity as to the boundaries between permitted and prohibited communications.[72] FDA's claim that the proposed rule would not impact the agency's policies set forth in non-binding guidance documents does not address FDA's obligation to ensure that those policies provide the clarity required under the First and Fifth Amendments.[73] Continuing to rely on ill-defined and

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[67] 85 Fed. Reg. at 59,723 (citing three final guidance and two draft guidance documents).
[68] *Id.*
[69] *Id.* n.7.
[70] MIWG, Comments on Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products; Availability of Memorandum; Reopening of Comment Period, Docket No. FDA-2016-N-1149, 28 (Apr. 19, 2017); MIWG, Citizen Petition, Docket No. FDA-2011-P-0512, 5-12 (July 5, 2011).
[71] *Fox Television Stations*, 567 U.S. at 253 (quoting *United States v. Williams*, 553 U.S. 285, 304 (2008)).
[72] *See, e.g.*, MIWG, Comments on Draft Guidance for Industry: "Distributing Scientific and Medical Publications on Unapproved New Uses – Recommended Practices," Docket No. FDA-2008-D-0053, 7-17 (May 2, 2014) (detailing concerns with FDA's revised draft guidance and the need to better align it "with constitutional principles" and "enhance clarity"); MIWG, Comments on Scientific Exchange and Responses to Unsolicited Requests, Docket Nos. FDA-2011-D-0868 and FDA-2011-N-0912, 1-2 (Mar. 27, 2012) (echoing PhRMA's concerns with terminology used in the draft guidance regarding unsolicited requests).
[73] Moreover, one of the guidance documents cited by FDA is the February 2014 revised draft guidance entitled "Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices." FDA never references the January 2009 *final* guidance document entitled, "Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and

non-binding guidance documents does not advance, and indeed only hinders, FDA's efforts to conform its regulatory framework to constitutional requisites. The practice of regulating these important matters through non-binding guidance documents, in addition to implicating constitutional concerns, impedes the public health by deterring manufacturers from communicating valuable information to health care professionals, payors, and other stakeholders.[74]

Although FDA has stated that it "does not intend" to use certain communications, as described in these non-binding guidance documents, as "evidence of intended use" in an enforcement action against the manufacturer, this language does not preclude action by FDA, DOJ, or other enforcement authorities (*e.g.*, state attorneys general) or categorically recognize the lawfulness of these communications. Accordingly, even if the proposed rule were finalized in its current form, FDA would still need to take further action to provide the necessary fair notice, as required under the Fifth Amendment, of which manufacturer communications do, and do not, create an intended use, which in turn, determines what speech is, and is not, permissible.

MIWG appreciates FDA's recognition in the preamble to the proposed rule that "knowledge in combination with conduct that falls within an acknowledged FDA 'safe harbor' would not be determinative of intended use." However, this language fails to provide adequate clarity and assurance to industry. First, much like the safe harbors described in guidance documents that the preamble incorporates by reference, this clarification would not be codified in FDA's binding regulations. Second, the "would not be determinative" phrasing is unhelpful because it implies that knowledge plus safe-harbored speech *can* be used to create an intended use so long as it is not "determinative." In this regard, the language takes back virtually everything that it purports to give. Third, FDA's reference to "conduct" that falls within an FDA safe harbor is confusing to the extent FDA is suggesting that a firm's actions undertaken pursuant to a safe harbor are conduct, rather than constitutionally protected speech. This position was rejected in litigation more than two decades ago.[75] To address these concerns, FDA should specify in the final rule that knowledge in combination with safe-harbored speech cannot create a new intended use.

Lastly, while the preamble to the proposed rule cites various safe harbors described in guidance documents, FDA makes no reference at all to scientific exchange, the one safe harbor expressly codified in the regulations for drugs.[76] As MIWG has previously advocated,[77] FDA

Approved or Cleared Medical Devices," which the February 2014 *draft* guidance proposed to revise. Under FDA's guidance document procedures, *see* 21 C.F.R. § 10.115(g), a revised draft guidance cannot supersede a previously issued final guidance.

[74] *See* MIWG, Comments on Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products; Availability of Memorandum; Reopening of Comment Period, Docket No. FDA-2016-N-1149, 28 (Apr. 19, 2017); MIWG, Comments on Draft Guidance for Industry: "Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products—Recommended Practices," Docket No. FDA-2014-D-0758, 2 (Aug. 25, 2014); MIWG, Citizen Petition, Docket No. FDA-2013-P-1079, 4-5 (Sept. 3, 2013).

[75] *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 59 (D.D.C. 1998) ("The distribution of enduring materials and sponsorship of CME seminars addressing and encouraging that conduct is speech. . . . There may certainly be a 'line' between education and promotion as regards a drug manufacturer's marketing activities, but that is the line between pure speech and commercial speech, not between speech and conduct.").

[76] 21 C.F.R. § 312.7.

[77] *See* MIWG, White Paper: Systemic, Societal, and Legal Developments Require Changes to FDA's Regulation of Manufacturer Speech, Docket No. FDA-2013-P-1079-0007, 50-54 (Oct. 31, 2014).

should confirm for both drugs and devices that scientific exchange is not relevant to intended use. The communication of truthful, non-misleading scientific and medical information is of substantial value to health care professionals, payors, and other stakeholders and furthers the public health. Accordingly, FDA should revise its regulations to ensure clear pathways for manufacturers to engage in robust scientific exchange. An interpretation of intended use that does not clearly recognize that FDA lacks statutory authority over scientific exchange would harm the public health, violate the First Amendment, fail to provide the necessary clarity required under the Fifth Amendment, and exceed the scope of FDA's statutory authority.[78]

C. FDA incorrectly asserts that relying on speech as evidence of intended use does not implicate manufacturers' First Amendment rights.

FDA asserts that it can "rel[y] on speech as evidence of intended use under the FD&C Act" without implicating manufacturers' First Amendment rights.[79] But FDA seeks to use speech to establish an intended use where there is no separate and independently illegal act. Where there would be no unlawful activity but for the consideration of constitutionally protected speech, relying on truthful, non-misleading speech by manufacturers about new uses of approved or cleared products to support a criminal conviction raises significant First Amendment concerns.

Using the standard set forth in the proposed rule, FDA could point to off-label speech, and off-label speech alone, as the requisite "evidence" of intended use. This could lead to enforcement actions where the prosecution of alleged misbranding of an approved or cleared product substantively amounts to prosecution of protected speech.[80] In dismissing First Amendment concerns, FDA fails to recognize that it seeks to rely on manufacturer speech to establish a violation of the FDCA.[81]

FDA asserts that such reliance on speech does not infringe First Amendment rights, based on *Wisconsin v. Mitchell*,[82] *Whitaker v. Thompson*[83] and *Nicopure Labs, LLC v. FDA*.[84] FDA's reliance on these cases is misplaced. *Mitchell* did not address speech concerning medical products at all, but rather dealt with speech in connection with the commission of aggravated battery and the application of a state penalty-enhancement statute.[85] The aggravated battery was a separate, independently illegal act, and the defendant's speech, which showed that the defendant selected

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[78] *See* MIWG, Comments on Scientific Exchange and Responses to Unsolicited Requests, Docket Nos. FDA-2011-D-0868 and FDA-2011-N-0912, 2 (Mar. 27, 2012).
[79] *See* 85 Fed. Reg. at 59,723.
[80] *See Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 196, 228 (S.D.N.Y. 2015) (holding that FDA's restrictions on manufacturer communications about unapproved uses "take[] aim at truthful, non-misleading speech").
[81] Indeed, the government has repeatedly recognized in other contexts that statutes which could be read to criminalize speech must be narrowly construed to avoid First Amendment violations. *See, e.g., United States v. Sineneng-Smith*, 140 S. Ct. 1575 (2020) ("In the Government's view, §1324(a)(1)(A)(iv) should be construed to prohibit only speech facilitating or soliciting illegal activity, thus falling within the exception to the First Amendment for speech *integral to criminal conduct*.") (emphasis added).
[82] 508 U.S. 476 (1993).
[83] 353 F.3d 947 (D.C. Cir. 2004).
[84] 944 F.3d 267 (D.C. Cir. 2019).
[85] 508 U.S. at 480-82.

the victim based on race, was used only as a basis for enhancing the criminal penalty imposed. Speech was not used, in and of itself, to change an otherwise lawful act into an unlawful act.

Additionally, neither *Whitaker* nor *Nicopure* involved speech with respect to new intended uses for approved or cleared medical products, but rather discussed speech as evidence of intended use in determining the FDA regulatory classification of products without *any* FDA approval or authorization.[86] The two applications of intended use are distinguishable. An approved or cleared medical product can generally be used or prescribed for off-label purposes as part of the practice of medicine.[87] As FDA itself recognizes in the proposed rule, "[h]ealth care providers sometimes prescribe or use approved or cleared medical products for unapproved uses when they judge that the unapproved use is medically appropriate for their individual patients."[88] Thus, in contrast to speech proposing an illegal transaction for a medical product that may not be lawfully used or prescribed, truthful, non-misleading speech regarding the lawful use of an approved or cleared medical product is lawful and afforded robust constitutional protection.

D. FDA's analysis of *Sorrell v. IMS Health Inc.* and other applicable First Amendment case law understates constitutional limitations on the Agency's authority.

The First Amendment discussion in the preamble to the proposed rule inappropriately minimizes the import of the Supreme Court's holding in *Sorrell v. IMS Health Inc.*, and fails to provide a robust *Central Hudson* analysis of FDA's use of speech as evidence of intended use.

FDA states in a footnote in the preamble to the proposed rule that several courts of appeals interpreting *Sorrell v. IMS Health Inc.* have "concluded that *Sorrell* did not overrule or fundamentally alter the *Central Hudson* analysis."[89] However, FDA does not grapple with the fact that the Supreme Court in *Sorrell* confirmed that a law that "disfavors marketing, that is, speech with a particular content" and "specific speakers, namely pharmaceutical manufacturers" is a content- and speaker-based restriction on speech.[90] The Court emphasized that such restrictions are subject to "heightened judicial scrutiny" and "presumptively invalid."[91] In finding the Vermont state law at issue unconstitutional, the Court noted that "the outcome [would be] the same whether a special commercial speech inquiry or a stricter form of judicial scrutiny is applied" and therefore there was "no need to determine whether all speech hampered by [the Vermont law] is commercial, as our cases have used that term."[92]

Perhaps because the Court in *Sorrell* did not address (and did not need to address under the facts at hand) the exact relationship between "heightened judicial scrutiny" and the long-recognized *Central Hudson* test for commercial speech, several circuit courts of appeals in the subsequent cases cited by FDA have taken the position that the *Central Hudson* test remains the

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[86] *Whitaker*, 353 F.3d at 952-53; *Nicopure*, 944 F.3d at 282-84.
[87] *See* MIWG, White Paper: Systemic, Societal, and Legal Developments Require Changes to FDA's Regulation of Manufacturer Speech, Docket No. FDA-2013-P-1079-0007, 9-11 (Oct. 31, 2014).
[88] 85 Fed. Reg. at 59,722.
[89] 85 Fed. Reg. at 59,724 n.11.
[90] *Sorrell v. IMS Health Inc.*, 564 U.S. 552, 564 (2011).
[91] *Id.* at 565, 571 (internal quotations omitted).
[92] *Id.* at 571.

standard for assessing the validity of a commercial speech restriction. Significantly, however, none of the cases relied upon by FDA deals with content- or speaker-based restrictions in the fields of medicine and public health, an area that the Supreme Court has recently reiterated is subject to heightened protection.[93] Instead, the cases cited by FDA relate to regulations on taxi and shared ride advertising,[94] billboard advertisements,[95] and liquid crystal display advertisements.[96] Accordingly, to the extent FDA reads these cases to suggest that *Sorrell* has no impact on the analysis of speech restrictions imposed on drug and device manufacturers under the First Amendment, that is inaccurate. Moreover, the Supreme Court's recent decision in *Barr v. American Association of Political Consultants, Inc.*—where five justices held that a commercial speech restriction violated the First Amendment because it was content-based and failed strict scrutiny—rejects the logic of the cases relied upon by FDA.[97]

At a minimum, *Sorrell* stands for the proposition that content- and speaker-based regulations—like FDA's restrictions on drug and device manufacturer speech—are presumptively unconstitutional and may only be sustained if the government is able to satisfy its heavy burden under the demanding judicial scrutiny that applies. Earlier this year, the Supreme Court underscored that "courts have generally been able to distinguish impermissible content-based speech restrictions from traditional or ordinary economic regulation of commercial activity that imposes incidental burdens on speech."[98] FDA must do so as well, and recognize that regulations that specifically target medical product manufacturers or specific speech in support of medical product advertising are subject to a higher standard of scrutiny than regulation of ordinary commercial speech.

Moreover, even prior to *Sorrell*, the Supreme Court had interpreted *Central Hudson* to require that a commercial speech restriction be narrowly tailored to directly advance a substantial government interest.[99] For decades, the Court has "made clear" that "if the Government could achieve its interests in a manner that does not restrict speech, or that restricts less speech, the Government *must do so*."[100] Although FDA asserts that its "consideration of speech as one type of evidence of intended use" satisfies the elements of the *Central Hudson* test,[101] FDA fails to provide any meaningful explanation for how its regulation of speech is narrowly tailored to achieve the government's purported interests. Specifically, FDA does not even discuss any "less speech-restrictive alternatives," much less explain why they would be inadequate to achieve the

[93] *See Barr v. Am. Ass'n of Political Consultants*, 140 S. Ct. 2335, 2347 (2020) (emphasizing that, "[i]n *Sorrell*, this Court held that a law singling out pharmaceutical marketing for unfavorable treatment was content-based" and therefore subject to heightened scrutiny); *Nat'l Inst. of Family and Life Advocates v. Becerra*, 138 S. Ct. 2361, 2366 (2018) (underscoring that the Supreme Court "has stressed the danger of content-based regulations 'in the fields of medicine and public health, where information can save lives'") (quoting *Sorrell*, 564 U.S. at 566).
[94] *See Vugo, Inc. v. City of New York*, 931 F.3d 42 (2d Cir. 2019).
[95] *See Missouri Broad. Ass'n v. Lacy*, 864 F.3d 295 (8th Cir. 2017).
[96] *See Retail Digital Network, LLC v. Prieto*, 861 F.3d 839 (9th Cir. 2017).
[97] 140 S. Ct. 2335, 2346-47 (plurality op.); *id.* at 2364 (Gorsuch. J., joined by Thomas, J., concurring in the judgement in part and dissenting in part) ("When the government seeks to censor speech based on its content, . . . its restrictions must satisfy strict scrutiny . . . .").
[98] *Barr*, 140 S. Ct. at 2347.
[99] *See, e.g.*, *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 371 (2002).
[100] *Id.* (emphasis added).
[101] 85 Fed. Reg. at 59,724.

government's interests.[102] The claims-based approach to intended use described in Section I, *supra*—while it is based on manufacturers' commercial speech—is far less speech-restrictive than FDA's proposed approach, in that the claims-based approach would permit manufacturers to convey non-promotional scientific and medical information for the benefit of healthcare professionals, payors, and other stakeholders.

In the case of speech that promotes a new use of an approved product, if that speech is truthful and non-misleading, FDA must show that no less restrictive alternatives are available and that restricting such speech directly advances the interests underlying the pre-market approval process. FDA cannot simply wish away these burdens based on the misguided theory that evidentiary use of protected speech does not even raise First Amendment concerns. To further address these issues, we again urge the Agency to complete its long-promised "comprehensive review" of regulations to assess alignment with constitutional and statutory requirements.[103]

Additionally, in its brief discussion of the *Central Hudson* elements, FDA cites a Canadian study.[104] As we have previously explained, the Canadian study does not support restrictions on manufacturer speech.[105] In summary, the Canadian study assessed the impact of off-label *uses*, not off-label *communications*, and the study's only relevance to questions about whether to restrict communications is its affirmative demonstration of the value that *additional* information sharing could have. The Canadian study found that off-label use supported by strong scientific evidence was associated with the same risk of adverse drug events as on-label use.[106] To this end, the study underscores the importance of providing information to health care professionals regarding scientifically supported off-label uses.[107] Any suggestion that the Canadian study will sustain FDA's restrictions on manufacturer speech under *Central Hudson* or otherwise is without foundation.

Restrictions on manufacturer speech, even assuming *Central Hudson* applies, must be narrowly tailored and supported by reasoned analysis, in light of the First Amendment implications of restricting speech. Without such a reasoned analysis, restrictions on speech are unconstitutional. FDA must accordingly not only recognize that *Sorrell* does impose heightened scrutiny (at least in certain cases), but also do more to justify its speech restrictions under *Central Hudson*, which does not—contrary to FDA's conclusory statements—give the agency *carte blanche*.

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[102] *See Caronia*, 703 F.3d at 167-68 (finding the government's "conclusory assertions" made "[i]n the absence of any support" about the inadequacy of less speech-restrictive alternatives to be "insufficient to sustain the government's burden of demonstrating that the proposed alternatives are less effective than its proposed construction of the FDCA in furthering the government interests identified").

[103] *See* Letter from Leslie Kux, Assistant Commissioner for Policy, to Alan R. Bennett, Joan McPhee, Paul Kalb, & Coleen Klasmeier, Docket Nos. FDA-2011-P-0512 and FDA-2013-P-1079, 8 (June 6, 2014).

[104] 85 Fed. Reg. at 59,724 n.12; *see* Tewodros Eguale et al., Association of Off-Label Drug Use and Adverse Drug Events in an Adult Population, 176 JAMA Internal Med. 55 (Nov. 2, 2015) [hereinafter "Canadian Study"].

[105] MIWG, Comments on Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products; Availability of Memorandum; Reopening of Comment Period, Docket No. FDA-2016-N-1149, 10-13 (Apr. 19, 2017)

[106] Canadian Study at 56-57.

[107] *See id.* at 60 (discussing inadequate dosing and contraindications information regarding off-label uses in drug labeling and physicians' difficulty in "keep[ing] up with rapidly changing medication information").

III. FDA's Proffered Examples of Evidence "Relevant to Establishing Intended Use" Are Unacceptably Vague or Overbroad and Fail to Provide Needed Clarity.

FDA in the preamble provides examples of four types of evidence relevant to establishing intended use: (1) express claims, (2) implied claims, (3) product characteristics and design, and (4) circumstances of the sale or distribution. While MIWG generally agrees that intended use comprises express and implied claims made in labeling, advertising, and analogous oral statements by or on behalf of a manufacturer, MIWG has concerns with the latter two categories described by FDA.

A. The characteristics and design of an approved or cleared medical product do not determine intended use.

With respect to product characteristics and design (which FDA proposes to codify in the regulations using the slightly different terms "design or composition"), FDA offers the following examples relevant to determining intended use: the known physiological effects of a product unapproved for any medical use, the known use of a product unapproved for any medical use, and the product's "design or technical features."[108] In the latter case, FDA describes only device-specific examples. Although FDA contends that the examples provide clarity for industry, they actually raise significant new questions and concerns.

First, FDA's consideration of product characteristics and design as evidence of intended use is inconsistent with the law. *See* Section I, *supra*.

Second, FDA's failure to specifically describe how the "design or composition" (the language of the proposed regulations) or the "product characteristics and design" (the alternative phrasing used in the preamble) of an approved or cleared product might be used in determining intended use creates significant ambiguity for industry. FDA offers no limiting principle for when the design or composition of an approved or cleared product may be considered in determining intended use. The examples offered by FDA suggest that unapproved products are the primary target of the proposed design or composition language. However, the text of the proposed regulation is not so limited, and the preamble also does not specify that limitation. Consequently, if the proposed rule were finalized in its current form, manufacturers of approved or cleared medical products would face the risk of FDA or DOJ (or a *qui tam* relator) attempting to assert a new intended use based *solely* on evidence of the design, composition, characteristics, or known effects of the product.

A theory of intended use based solely on the design or composition of a product would be inconsistent with the objective intent standard of the regulations, especially in situations where the design or composition evidence conflicts with the uses suggested by the manufacturer in promotional claims. For example, if a medical product is approved and promoted only for *Use A*, for which it is appropriately designed, it should not matter that its design or mechanism of action also permits the product to be used for *Use B.* The manufacturer should not be at risk of the government asserting the existence of a new intended use for *Use B* based solely on uses enabled by the product's design. If the proposed rule is finalized without revision, manufacturers will not

[108] 85 Fed. Reg. at 59,725.

know whether or under what circumstances the design or composition of their products will create a new intended use. Based on a literal reading of the proposed regulations, a manufacturer of an approved or cleared medical product could at least theoretically face an enforcement action merely because its product works in a manner that may also be effective for unlabeled uses. In extreme cases, if the government failed to disavow this illogical and legally problematic theory of intended use, manufacturers might be altogether discouraged from even *developing* products that, based on their design, are likely to be effective for multiple uses.

For these reasons, FDA should remove the "design or composition" language from the proposed rule.

B. FDA's example of "repeated proactive detailing" of health care professionals whose patients do not fall within a product's labeled population is unclear and conflicts with prior agency statements.

With respect to circumstances surrounding distribution, FDA provides an example of a firm's "repeated proactive detailing" and delivery of complimentary samples to a health care provider whose patient population is not within the product's approved population. This example suggests that detailing and providing samples to health care professionals who do not ordinarily treat patients within a product's labeled population can create a new intended use, even if the firm's communications with the health care professionals are entirely consistent with the approved labeling.

This interpretation would be inconsistent with the position previously taken by the Government in litigation. Specifically, in defending a First Amendment challenge brought by a drug manufacturer, FDA stated that it does not consider a manufacturer's truthful and non-misleading speech concerning the *approved* use of an FDA-approved drug to health care professionals whose patient populations fall outside the FDA-approved patient population as evidence of a new intended use.[109] FDA essentially confirmed that so long as a manufacturer's speech remains on-label, the fact that the manufacturer is communicating with health care professionals who treat patients outside of the product's approved patient population would not by itself create a new intended use.

FDA should clarify, consistent with its position in the *Par* litigation, that the example of "repeated proactive detailing" in the preamble to the proposed rule would not create a new intended use if the firm's communications with the health care professionals are consistent with the approved labeling.

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[109] Def.'s Mem. Support Mot. Dismiss or S.J. and Opp'n to Mot. Prelim. Inj. at 17-18, *Par Pharmaceutical, Inc. v. United States*, No. 1:11-cv-01820 (D.D.C. Jan. 11, 2012) ("The government has not threatened to bring, and has no intention of bringing, an enforcement action based exclusively on truthful and non-misleading speech concerning the approved use of [Par's drug] to healthcare professionals in the settings and circumstances described in Par's complaint [which include 'potentially off-label settings']."); Decl. of Rachel E. Sherman ¶¶ 14, 16, *Par Pharmaceutical, Inc. v. United States*, No. 1:11-cv-01820 (D.D.C. Jan. 11, 2012) ("In FDA's view, Par's truthful and non-misleading speech concerning the approved use of [Par's drug] to the healthcare professionals identified in the [complaint and motion for preliminary injunction] would not establish Par's objective intent that [Par's drug] be used for an unapproved use.").

IV. The Examples of Evidence "That, Standing Alone, Are Not Determinative of Intended Use" Cause Further Confusion Instead of Providing Clarity.

The examples-based approach in Section V.C. of the preamble has the effect of understating the latitude a manufacturer has in the current regulatory environment to provide accurate information about unlabeled uses. The default rule is not the broad "evidentiary" approach reflected in the proposed rule, in which claims are one of many sources to which the government can point as part of an effort to establish liability, and a manufacturer must attempt to conform its business activities to a combination of grace-and-favor safe harbors described by FDA in guidance. Rather, the rule is the claims-based interpretation. Under the former approach, no regulated firm would ever be able to completely limit the scope of its own legal exposure. Under the latter, accurate scientific information could be shared within the health care delivery system; manufacturers could engage in reasonable business activity such as internal planning meetings and appropriate unregulated external communications (*e.g.*, to investors); and marketed products could be put to clinically appropriate unlabeled uses by health care professionals and patients.

As described above, MIWG appreciates FDA's confirmation in the preamble accompanying the proposed rule that a firm would not be regarded as "intending an unapproved new use" for an approved drug or approved or cleared device based solely on that firm's knowledge that such drug or device was being prescribed or used by health care providers for such use.[110] However, inconsistent language in the preamble creates the potential for confusion. Specifically, the preamble states that the new regulatory language is being added "to clarify that a firm's knowledge that health care providers are prescribing or using its approved or cleared medical product for an unapproved use would not, by itself, *automatically* trigger obligations for the firm to provide labeling for that unapproved use."[111] The use of "automatically" could be interpreted to mean that knowledge, "by itself," can still be evidence of a new intended use, even if the determination is not "automatic[]." Additionally, the reference to "health care providers" in the proposed regulations is unnecessarily limiting and does not account for over-the-counter or nonprescription drugs and devices that may be used by individual consumers without the involvement of a health care professional or prescription products used by patients in a manner that does not accord with labeled directions (*e.g.*, where a patient unilaterally departs from the labeled and prescribed dosing schedule).

Other examples in the preamble purport to give manufacturers permission to engage in certain types of speech that are already permitted, and have not been the source of uncertainty for many years. For example, merely following the social media account of a patient advocacy organization tied to a new use[112]—whether the manufacturer is investigating its approved product for that use or not—is simply nowhere near making a claim with respect to a new use and has never been identified as potentially even relevant to intended use, even under FDA's newly devised alternative interpretation. The other examples are similarly illusory, whether because they were never at issue or because FDA had already affirmed that the speech was permissible. Moreover,

[110] 85 Fed. Reg. at 59,729.
[111] *Id.* at 59,720 (emphasis added).
[112] *Id.* at 59,726.

in some respects the examples are more limited than corresponding prior FDA statements. Specifically:

- An internal company meeting at which an officer presents sales projections reflecting potential sales for an off-label use does not create a new intended use and should never be regarded as relevant to intended use under the Agency's improper "evidentiary" approach—whether or not the use is "widely recognized as the standard of care."[113]
- Disclosures and presentations to the investment community are not within FDA's purview, regardless of whether the communications constitute "required disclosures" to the SEC.[114]
- A manufacturer is permitted to provide a summary of clinical trial results to clinical trial participants to "acknowledge their contributions to scientific and medical advancement (not to inform prescribing and use decisions)."[115] FDA had already settled litigation against *Amarin* on terms that expressly allowed this type of speech and even more.[116]
- The dissemination of "safety information about an unapproved use to health care providers to minimize risk to patients" alone "would not ordinarily be dispositive evidence of a new intended use."[117] But FDA had already recognized that manufacturers had that latitude.[118] And the preamble example creates further confusion by implying that the scope of permissible communication about risks associated with unlabeled use is limited to occasions on which the official FDA-approved labeling for the drug *already* "warn[s] of potential risks related to the unapproved use in general terms . . . ."[119]

Intended use also should not be established, determined, or created by any of the following:

- A "firm's directions to their sales forces,"[120] because information regarding investigational products and unlabeled uses of approved or cleared products may be provided to individuals involved in sales for a range of legitimate reasons (*e.g.*, to explain the role of a specific marketed product in a company's broader therapeutic portfolio, including products under development for subpopulations in the same disease state);
- The dissemination of clinical practice guidelines (CPGs), whether alone or in combination with knowledge (from "sales and distribution metrics" or otherwise) that the product is being used off-label in accordance with such guidelines,[121] even if the CPGs do not satisfy every recommendation of FDA's draft guidance, because, as MIWG and others have

[113] *Id.*
[114] *Id.*
[115] *Id.*
[116] *See* Stipulation & Order of Settlement, *Amarin Pharma, Inc. v. FDA*, No. 1:15-cv-3588-PAE (S.D.N.Y. Mar. 8, 2016).
[117] 85 Fed. Reg. at 59,725.
[118] Decl. of Robert Temple, *Allergan v. United States*, No. 09-cv-01879 (D.D.C. Dec. 11, 2009).
[119] 85 Fed. Reg. at 59,726.
[120] *Id.* at 59,723.
[121] *Id.* at 59,725.

previously commented, those recommendations are unduly restrictive and chill highly valuable scientific speech.[122]

If the final rule were consistent with the claims-based interpretation of intended use, then these ambiguities would be resolved and FDA would explain in the accompanying preamble language that these examples reflect permitted expression that is outside the scope of intended use. In any case, FDA should state definitively in the final rule that knowledge "would not, by itself, trigger" labeling obligations for the new use. MIWG further requests that FDA clarify its analysis of the examples set forth above, and in particular describe these examples of permissible communications accurately and without the additional limitations that have been identified in our comments.

V. Conclusion

MIWG appreciates FDA's changes since the 2017 final rule, including the elimination of the "totality of the evidence standard" and the recognition that knowledge of off-label use, either standing alone or in combination with safe-harbored speech, will not be regarded as evidence of a new intended use. However, the proposed rule continues to fall short. The proposed rule reflects an approach to intended use that exceeds the scope of FDA's statutory authority and implicates the First and Fifth amendments by chilling the communication of truthful, non-misleading information and failing to provide fair notice of permissible and impermissible speech. FDA should revise the intended use regulations in a manner consistent with the statutory and constitutional requirements we have described. Additionally, FDA should make clear, pending resolution of the new rulemaking, that the Agency will follow the claims-based approach to intended use.

[122] *See* Comments of the Medical Information Working Group, Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products; Availability of Memorandum; Reopening of Comment Period (Docket No. FDA-2016-N-1149) (Apr. 19, 2017), at 16–17.

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