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July 18, 2017

Via Electronic Submission

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

MEDICAL INFORMATION WORKING GROUP
COMMENTS ON FDA'S "INTENDED USE" FINAL RULE
(Docket No. FDA-2015-N-2002)

These comments are submitted on behalf of the Medical Information Working Group (MIWG), in response to the Federal Register notice published by the Food and Drug Administration (FDA) on March 20, 2017 (82 Fed. Reg. 14,319). The MIWG is a coalition of medical product manufacturers focused on improving the regulatory and enforcement environment affecting manufacturer communications about drugs and medical devices, including communications about development-stage products and new uses of lawfully marketed products.[1] FDA's March 20 notice was published in response to a Petition to Stay and for Reconsideration filed by the MIWG, the Pharmaceutical Research and Manufacturers of America (PhRMA), and the Biotechnology Innovation Organization (BIO) on February 8, 2017 ("Petition for Stay").[2]

The Petition for Stay objected to FDA's final rule changing the regulatory definitions of intended use for drugs and medical devices, which was published on January 9, 2017 and scheduled to become effective thirty days later, on February 8, 2017 (the Final Rule).[3] As the

[1] The members of the MIWG are: Allergan plc; 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 Corporation; Pfizer Inc.; Sanofi US; and Samumed, LLC. The MIWG's prior submissions to FDA are available at www.miwg.org.

[2] MIWG, PhRMA & BIO, Petition to Stay and for Reconsideration, Docket No. FDA-2015-N-2002-1977 (Feb. 18, 2017).

[3] Clarification of When Products Made or Derived from Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses," 82 Fed. Reg. 2,193 (Jan. 9, 2017).

Petition for Stay explained, the Final Rule raised two significant legal issues. First, the Final Rule exceeds the scope of FDA's authority under the Federal Food, Drug, and Cosmetic Act (FDCA). Second, FDA violated the Administrative Procedure Act (APA) by adopting the new "totality" language without adequate notice. The Petition for Stay requested a stay to permit FDA to reconsider the Final Rule. In the March 20 notice, FDA stated that the "issues raised by the petition and similar concerns" justified extending the effective date of the Final Rule until March 19, 2018, and requested "full public comments on these underlying issues."[4]

For the reasons discussed below, FDA should remove from the Final Rule (1) the "totality" language, (2) the last sentence relating to "knowledge," as originally provided in the Proposed Rule, (3) the reference to "circumstances surrounding distribution," and (4) any other language that suggests FDA may define intended use based on evidence other than promotional claims. Our comments in this document focus on the following points:

- The public health consequences of the Final Rule are significant. Long-standing FDA policies facilitate manufacturer dissemination of off-label information in certain carefully defined circumstances. These policies, as FDA has recognized, advance patient care and promote the public health. The "totality of the evidence" standard, however, arguably would provide a basis for asserting liability under the FDCA based solely on manufacturer communications that are permitted under these pre-existing policies. As a result, manufacturers would have to either discontinue communications practices that even FDA has acknowledged advance public health objectives or continue those practices at risk.

- The First and Fifth Amendments are aligned with these public health considerations because they independently reinforce the need for FDA to avoid unnecessarily chilling the communication of medical information that is valuable for patient health. The "totality of the evidence" standard would raise important constitutional concerns by chilling the communication of truthful, non-misleading information about medical products. The First Amendment imposes significant limitations on the government's ability to regulate truthful, non-misleading manufacturer speech, in recognition of the fact that the public interest is served by more of this speech, rather than less. The Fifth Amendment also requires that the boundaries between permissible and impermissible activities be clearly drawn. The "totality of the evidence" standard does not satisfy these constitutional dictates.

- The Final Rule is also legally problematic because it radically departs from the well-established statutory interpretation of intended use reflected in the applicable legal

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[4] The comment request in the March 20 notice is broad, encompassing both four specific sets of questions and "any other pertinent comments or information[.]" 82 Fed. Reg. at 14,322. On April 5, 2017, the MIWG, PhRMA, and BIO requested an extension of the May 19, 2017 deadline for the submission of comments on the March 20 notice because of the scope, complexity, and importance of the issues involved. MIWG, PhRMA & BIO, Request for Extension, Docket No. FDA-2015-N-2002-1988 (Apr. 5, 2017). In particular, we cited the nexus between the intended use rulemaking proceeding and the manufacturer communication proceeding, which FDA has also acknowledged. *E.g.*, 82 Fed. Reg. at 14,321 n.3.

authorities, including the legislative history. In addition, the all-encompassing "totality" standard would thwart the orderly operation of the regulatory scheme.

- Despite FDA's assertion to the contrary in the Final Rule preamble, a "totality" standard is not necessary to prevent unscrupulous firms from evading regulation. As we explain below, under the traditional, claims-based interpretation of intended use, FDA would still be able to protect the public health effectively, including in the scenarios outlined in the preamble.

As noted in the Petition for Stay, FDA's interpretation of intended use raises challenging First Amendment questions. FDA has commenced a "comprehensive review" of the regulatory scheme to address these questions. The agency's review has involved a public hearing and, more recently, publication of a lengthy memorandum on the application of First Amendment principles to FDA's regulation of manufacturer speech.[5] The MIWG has submitted extensive comments to FDA on these issues, including intended use.[6] Our comments incorporate by reference both our prior submissions on intended use and the Petition for Stay.

I. The Final Rule Has Significant Public Health Implications Because It Would Chill Communications That Are Important For Patient Care

A. The Final Rule Would Undermine The Established Safe Harbors For The Communication Of Valuable Medical And Scientific Information

The public interest is best served when decisions regarding uses of medical products are informed by as much truthful, accurate, and non-misleading information as possible.[7] Manufacturers are well positioned to provide such information, including information that is not in a product's approved labeling, because they often have the earliest, surest access to it. They also have the resources and infrastructure to share this information in a timely and efficient manner. Consequently, manufacturers are well-positioned to provide physicians with accurate

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[5] *See* Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products; Public Hearing; Request for Comments, 81 Fed. Reg. 60,299 (Sept. 1, 2016); FDA Memorandum, Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products, Docket No. FDA-2016-N-1149 (Jan. 2017).

[6] *See, e.g.*, 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 (Apr. 19, 2017); MIWG, Comments on 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. FDA-2015-N-2002 (Nov. 24, 2015); MIWG, White Paper: Systemic, Societal, and Legal Developments Require Changes to FDA's Regulation of Manufacturer Speech, Docket No. FDA-2013-P-1079 (Oct. 31, 2014); MIWG, Citizen Petition, Docket No. FDA-2013-P-1079 (Sept. 3, 2013).

[7] *See* Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices, 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").

and up-to-date scientific and medical information.[8]

FDA has long recognized the public health importance of information about off-label use. Among many other statements, in 1992, FDA's then-Associate Commissioner for Health Affairs emphasized the importance of the earliest possible dissemination of information about new uses, writing that "the very latest information that can be of value to physicians . . . must be made available as soon as possible. Frequently, unlabeled use information is extremely important."[9] Similarly, in 1998, FDA stated that "[g]ood medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgment."[10] More recent guidance documents from FDA have stated that "off-label uses or treatment regimens may be important and may even constitute a medically recognized standard of care."[11] Moreover, FDA has recognized the central role *of manufacturers* in sharing information about off-label uses, observing that "[s]cientific departments within regulated companies generally maintain a large body of information on their products."[12] As FDA's prior public pronouncements have made clear, manufacturer dissemination of information about off-label uses can be necessary for the advancement of patient care and public health—and the earlier such information is disseminated, the better.

Over many years, FDA has established communications policies that reflect the public value of off-label information and facilitate its dissemination.[13] These policies recognize that

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[8] *See* Reports of the Council on Scientific Affairs (1997); *see also More Information for Better Patient Care: Hearing of the Senate Comm. on Labor and Human Resources*, 104th Cong. 81 (1996) (statement of Dr. Gregory H. Reaman, Director, Medical Specialty Services, Children's National Medical Center) ("Pharmaceutical and biotechnology companies obviously have an interest in supporting new uses of their products, but they also happen to be in the best position to share information with the physician community at the earliest possible time, when it may really make a difference in treatment options.").

[9] Stuart Nightingale, *Unlabeled Uses of Approved Drugs*, 26 DRUG INFO. J. 141, 145 (1992).

[10] FDA, "Off-Label" and Investigational Use of Marketed Drugs, Biologics, and Medical Devices – Information Sheet (1998); *see also* Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices, 63 Fed. Reg. 31,143, 31,153 (proposed June 8, 1998) ("FDA has long recognized that in certain circumstances, new (off-label) uses of approved products are appropriate, rational, and accepted medical practice.").

[11] *See* FDA, Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs or Cleared Medical Devices (Jan. 2009); FDA, Draft Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices (Dec. 2011).

[12] Citizen Petition Regarding the Food and Drug Administration's Policy on Promotion of Unapproved Uses of Approved Drugs and Devices; Request for Comments, 59 Fed. Reg. 59,820, 59,823 (Nov. 18, 1994).

[13] *See, e.g.*, FDA, Revised Draft Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses — Recommended Practices, 6 (Feb. 2014) ("[T]he public health may benefit when health care professionals receive truthful and non-misleading scientific or medical publications on unapproved new uses."); FDA, Draft Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices, 3 (Dec. 2011) (". . . [I]t can be in the best interest of public health for a firm to respond to unsolicited requests for information about off-label uses . . . .").

manufacturers can lawfully provide scientifically sound off-label use information in accordance with the following "safe harbors": (1) "scientific exchange,"[14] (2) responses to unsolicited requests,[15] (3) sponsorship of continuing medical education (CME) and other "scientific and educational activities,"[16] and (4) dissemination of medical journal articles and scientific or medical reference publications to prescribers and healthcare entities.[17] With the exception of scientific exchange (and then only for drugs), all of the safe harbors appear in non-regulatory "advisory" or "guidance" documents.[18] Although FDA has stated that it "does not intend" to use such communications as evidence of intended use in a misbranding or other regulatory action against the manufacturer,[19] that assurance does not preclude enforcement action or categorically recognize the lawfulness of these communications.

At the same time, the Final Rule would codify the "totality" standard in binding regulations in two locations—21 C.F.R. § 201.128 for drugs and 21 C.F.R. § 801.4 for medical devices. Because regulations have the force of law and guidance typically does not, the Final Rule creates a significant risk that manufacturer communications that are within the scope of the safe harbors nevertheless would be cited by FDA in an enforcement action. The Final Rule would also give the Department of Justice (DOJ) and/or a *qui tam* relator leverage to allege that safe-harbored communications are relevant to intended use by asserting that the safe harbors are superseded by the amended definition of intended use. The potential for FDA's capacious definition of intended use to harm significant public health interests is, therefore, not speculative.

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[14] 21 C.F.R. § 312.7(a).

[15] 59 Fed. Reg. at 59,823; *see also* FDA, Draft Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices, 3 (Dec. 2011).

[16] Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64,074 (Dec. 3, 1997).

[17] FDA, Revised Draft Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses — Recommended Practices (Feb. 2014); FDA, Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices (Jan. 2009).

[18] *See, e.g.*, notes 14-17, *supra*; *see also* FDA, Draft Guidance for Industry: Medical Product Communications That Are Consistent With the FDA-Required Labeling (Jan. 2017); FDA, Draft Guidance for Industry: Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products (June 2014).

[19] *See, e.g.*, FDA, Revised Draft Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses — Recommended Practices, 6 (Feb. 2014) ("Consistent with longstanding FDA policy and practice, if manufacturers distribute scientific or medical publications as recommended in this guidance, FDA *does not intend* to use such distribution as evidence of the manufacturer's intent that the product be used for an unapproved new use.") (emphasis added); FDA, Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices (Jan. 2009) ("[I]f a manufacturer follows the recommendations . . . of this guidance, FDA *does not intend* to consider the distribution of such medical and scientific information in accordance with the recommendations in this guidance as establishing intent that the product be used for an unapproved new use.") (emphasis added).

Even the preamble accompanying the Final Rule undermines the existing safe harbors for manufacturer communications. According to the preamble, "evidence relevant to intended use" includes "manufacturer statements *in a variety of contexts*," including types of communications commonly used to convey safe-harbored information.[20] In particular, the preamble identified "press statements; official or unofficial statements made by corporate officials; [and] statements made in social media and other online arenas," as communications covered by the Final Rule.[21] All of these categories include communications that are commonly regarded as within the scope of at least one existing FDA safe harbor.[22] Under long-standing FDA regulations, a preamble constitutes an "advisory opinion" and therefore has binding legal effect.[23] As a result, a manufacturer seeking to rely on a safe harbor set forth in a guidance document would have to consider the risk that FDA, DOJ, or a *qui tam* relator would cite the broad preamble language to support legal action alleging that the manufacturer has misbranded its product through ostensibly safe-harbored communications.

FDA has repeatedly promised to accommodate both the need for robust enforcement of the FDCA and the need for manufacturers to have reasonable latitude to provide information protected by these pre-existing safe harbors.[24] The only way to accomplish that dual objective is for the agency to limit "intended use" so that it does not encompass scientific exchange and other safe-harbored speech. As we said in our 2012 comments on FDA's scientific exchange notice,[25] "[t]o assure appropriate latitude for scientific exchange, FDA must clarify the scope of its intended use regulation to reflect the authoritative legislative history and the relevant case

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[20] 82 Fed. Reg. at 2,207 (emphasis added). The preamble refers to not only manufacturer communications as potential evidence but also a seemingly unlimited and ultimately undefined range of sources, including "evidence of a manufacturer's marketing plans," "evidence of a manufacturer's . . . directions to its sales force," "evidence of the well-known uses and abuses of its products," "circumstantial evidence relating to the sale and distribution of the product," evidence that a product "contain[s] a pharmacological ingredient," "internal firm documents and circumstances surrounding the sale of products," "consumer intent," "evidence of claims that were never communicated to the public," and the "overall circumstances."

[21] *Id.*

[22] Manufacturer press releases, for example, are often issued under the "scientific exchange" rule, 21 C.F.R. § 312.7.

[23] 21 C.F.R. § 10.85.

[24] *See, e.g.,* Citizen Petition Regarding the Food and Drug Administration's Policy on Promotion of Unapproved Uses of Approved Drugs and Devices; Request for Comments, 59 Fed. Reg. 59,820, 59,823 (Nov. 18, 1994); *see also* Advertising and Promotion; Guidances, 61 Fed. Reg. 52,800, 52,800 (Oct. 8, 1996) (noting that agency policies should "strike the proper balance between the need for an exchange of reliable scientific data and information within the health care community, and the statutory requirements that prohibit companies from promoting products for unapproved uses."); Draft Policy Statement on Industry-Supported Scientific and Educational Activities; Notice, 57 Fed. Reg. 56,412, 56,412 (Nov. 27, 1992).

[25] Communications and Activities Related to Off-Label Uses of Marketed Products and Use of Products Not Yet Legally Marketed; Request for Information and Comments, 76 Fed. Reg. 81,508 (Dec. 28, 2011).

law."[26] By clearly excluding safe-harbored communications from the definition of intended use, FDA's regulatory framework would respect its own long-standing safe harbors and facilitate the dissemination of scientifically sound information that is important for patient care.

B. The Final Rule's Impact On Manufacturer Communications Also Implicates Significant Constitutional Considerations That Reflect The Public Interest In Accurate, Scientifically Sound Communications

FDA's interest in protecting the public health is undeniable, as is the agency's recognition that the communication of truthful and non-misleading information about off-label uses can help support informed decision-making in the health care system. These public health interests are aligned with the First Amendment, which is also premised on the recognition that the public interest is served by more, rather than less, truthful and non-misleading speech.

The First Amendment requires FDA to enforce the FDCA through "limited and targeted regulations on speech,"[27] in keeping with the public health benefits associated with access to accurate, scientifically sound medical information. A broad "totality" standard that requires manufacturers to self-censor and avoid engaging in truthful, non-misleading speech for fear that such speech will be used as evidence of a new intended use does not satisfy the tailoring requirements under either the *Central Hudson*[28] test or the "heightened scrutiny" standard announced in *Sorrell v. IMS Health.*[29]

Furthermore, the Fifth Amendment requires FDA to provide sufficient clarity to manufacturers to ensure that they received "fair notice of what is prohibited."[30] "[R]igorous adherence" to the notice requirements of the Fifth Amendment is particularly "necessary to ensure that ambiguity does not chill protected speech."[31] Because the "totality" standard does not clearly define what speech may serve as evidence of an intended use—and suggests, due to its breadth, that *all* speech can be used—it does not provide the clarity required by the Fifth Amendment. The fact that a codified "totality" standard would potentially conflict with various "safe harbors" established by FDA further exacerbates the lack of clarity, and attendant Fifth Amendment concerns, presented by the Final Rule.

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[26] MIWG, Comment, Docket No. FDA-2011-N-0912 (Mar. 27, 2012) at 9 n.21 (citing S. Rep. No. 361, 74th Cong., 1st Sess. 4 (1935); *Brown & Williamson Tobacco Corp. v. FDA*, 153 F.3d 155, 163 (4th Cir. 1998)).

[27] *United States v. Caronia*, 703 F.3d 149, 168-69 (2d Cir. 2012).

[28] *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n*, 447 U.S. 557 (1980).

[29] 564 U.S. 552, 564 (2011).

[30] *FCC v. Fox Television Stations, Inc.*, 132 S. Ct. 2307, 2318 (2012).

[31] *Id.* at 2317.

II. According To The Legislative History, The Case Law, The Statutory Language, And The Structure of The Statute, Intended Use Cannot Be Determined Based On A Broad "Totality" Standard

As the Petition for Stay explained, the expansive "totality" approach taken by FDA in the Final Rule would both frustrate the orderly operation of the statutory scheme and interject FDA into areas of federal regulation that the law reserves to other federal regulators. On the other hand, "intended use" is a foundational FDCA concept that dates back more than a century and has always been understood to concern the claims made by the product's manufacturer in the marketplace. This interpretation is embodied in legislative history that the courts have recognized as authoritative.[32] Moreover, as discussed below, only a claims-based interpretation of intended use respects the governing case law. As a result, the Final Rule must be revised to remove the "totality" language and codify the claims-based interpretation.

The legislative history clearly reflects the intention of the FDCA's sponsors to tie intended use to representations made by the manufacturer.[33] Committee reports in 1934 and 1935 likewise explained that

> 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. For example, the manufacturer of a laxative which is a medicated candy or chewing gum can bring his product within the definition of drug and escape that of food by representing the article fairly and unequivocally as a drug product.[34]

Federal courts have accumulated an extensive body of case law on intended use under the FDCA—without ever having defined that key concept according to a "totality" standard. As early as 1920,[35] courts were defining "intended use" based on manufacturers' promotional claims. In 1953, the Second Circuit held that claims were essential to establish an intended use.[36] "The real test is how . . . this product [is] being sold[.]"[37] Indeed, courts "have always read the . . . statutory definitions employing the term 'intended' to refer to *specific* marketing

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[32] *United States v. 46 Cartons . . . Fairfax Cigarettes*, 113 F. Supp. 336, 337 (D.N.J. 1953).

[33] *See, e.g., Hearings on S. 2800 before the Comm. on Commerce*, 73d Cong., 517-18 (Feb. 27 to Mar. 3, 1934) (colloquy between Senator Royal S. Copeland and Walter G. Campbell) (explaining that a chiropractor's table would not be subject to the act unless the manufacturer "were to ship that table into interstate commerce, and say that that table would cure various ills").

[34] S. Rep. 493, 73d Cong. 2d Sess., 3 (1934); S. Rep. 361, 74th Cong., 1st Sess., 4 (1935).

[35] *Bradley v. United States*, 264 F. 79 (5th Cir. 1920).

[36] *FTC v. Liggett & Myers Tobacco Co.*, 203 F.2d 955 (2d Cir. 1953) (per curiam), *aff'g* 108 F. Supp. 573 (S.D.N.Y. 1952).

[37] *United States v. Nutrition Serv., Inc.*, 227 F. Supp. 375, 386 (W.D. Pa. 1964), *aff'd*, 347 F.2d 233 (3d Cir. 1965).

representations,"[38] and "*no court has ever found* that a product is 'intended for use' or 'intended to affect' within the meaning of the [FDCA] absent manufacturer *claims* as to that product's use."[39] The claims-based understanding of intended use has also been accepted "as a matter of statutory interpretation."[40]

The courts are so fixed in the principle that claims determine intended use that they have held that FDA must demonstrate that promotional claims have been distributed for them to establish an intended use. The seminal case is *United States v. Articles of Drug for Veterinary Use*,[41] in which the United States Court of Appeals for the Eighth Circuit considered the intended uses of six products made from colostrum. The Government pointed to written materials seized from the manufacturer, including product brochures, pamphlets, and advertisements claiming that the product increased young animals' chance of survival, improved their circulatory flow, reduced the severity of pneumonia, and stimulated digestion. The Court held that the materials were relevant to intended use *only* if (1) they were promotional in nature, (2) they were actually distributed to customers, and (3) customers were currently relying on them.[42] Because factual disputes existed with regard to all of those issues, the Eighth Circuit affirmed the district court's denial of the Government's motion for summary judgment.[43]

FDA's proposed "totality of the evidence" standard would frustrate the orderly operation of the statutory scheme. The agency has made clear that, under the Final Rule, the government could continue to rely upon a manufacturer's knowledge of off-label use when determining intended use.[44] Virtually every manufacturer has such knowledge, because manufacturers have access to a broad range of information about the uses to which their products are put in clinical

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[38] *Am. Health Prods. Co. v. Hayes*, 574 F. Supp. 1498, 1505 (S.D.N.Y. 1983) (emphasis added) (citations omitted), *aff'd on other grounds*, 744 F.2d 912 (2d Cir. 1984).

[39] *Brown & Williamson Tobacco Corp. v. FDA*, 153 F.3d 155, 163 (4th Cir. 1998) (emphasis added) (*citing Coyne Beahm v. FDA*, 966 F. Supp. 1374, 1390 (M.D.N.C. 1997)), *aff'd on other grounds*, 529 U.S. 120 (2000).

[40] *ASH v. Harris*, 655 F.2d 236, 239 (D.C. Cir. 1980).

[41] 50 F.3d 497 (8th Cir. 1995).

[42] *Id.* at 500-501.

[43] *Id. See also* Petition for Stay, *supra* note 2 at 16 (discussing the cases that address this issue, including those cited by FDA in the preamble to the Final Rule); *United States v. Undetermined Quantities of an Article of Drug Labeled as "EXACHOL,"* 716 F. Supp. 787, 791 (S.D.N.Y. 1989) (requiring evidence that customers continued to rely on therapeutic claims made in literature previously marketed with the product); *United States v. Pro-Ag, Inc.*, 796 F. Supp. 1219, 1225 (D. Minn. 1991), *aff'd*, 968 F.2d 681 (8th Cir. 1992) (claims made in promotional materials that defendant no longer distributed were admissible only if the Government could demonstrate that defendant's customers purchased the products at issue in reliance on those materials).

[44] 82 Fed. Reg. at 2,206.

practice, including off-label uses.[45] The government could rely on this knowledge—as well as any other fact, even if circumstantial or only marginally relevant—to find that a manufacturer intended a new use for its product. Unless the concept of intended use is firmly grounded in the claims-based interpretation, a manufacturer under these circumstances would be subject to the requirement to provide labeling that "accords with" the off-label uses.[46] The practical effect would be to prohibit the sale or marketing of the drug, even for its approved use, until further FDA approvals could be secured. "[T]his course of events" clearly would "frustrate the longstanding practice of Congress, the FDA, and the courts not to interfere with physicians' judgments and their prescription of drugs," whether for "on" or "off" label uses.[47] The agency's proposed rule would have begun to address this issue by removing the knowledge prong from the regulations, but the Final Rule's introduction of the totality standard not only reintroduces that language but indeed exacerbates the problem by expanding the scope of "intended use" to include any and all sources of evidence deemed relevant by FDA in any given case.

FDA's "totality" interpretation also interjects FDA into areas of federal regulation that the law reserves to other regulators. Statutes administered by the Consumer Product Safety Commission (CPSC) explicitly exclude products that qualify as drugs or medical devices under the FDCA.[48] Where jurisdiction could be interpreted as overlapping, CPSC and FDA have also determined the extent of their respective fields of regulatory authority based on the claims-based interpretation of intended use. Thus, for example, the agencies have agreed that an air cleaner is regulated by FDA if "medical claims are made for the product" and by CPSC if such claims are absent.[49] If FDA were to change its longstanding approach and interpret intended use based on

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[45] *See, e.g.*, *Sigma-Tau Pharms. v. Schwetz*, 288 F.3d 141, 145 n.2 (4th Cir. 2002) (referring to "'readily available'" market data put forth by a manufacturer demonstrating that 80 percent of the actual use of the manufacturer's drug was off-label).

[46] 21 C.F.R. §§ 201.128, 801.4.

[47] *See Sigma Tau*, 288 F.3d at 147 (citing *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1496 (D.C. Cir. 1996); *Rhone-Poulenc Rorer Pharm., Inc. v. Marion Merrell Dow, Inc.*, 93 F.3d 511, 514 n.3 (8th Cir. 1996)); *see also Millet, Pit & Seed Co. v. United States*, 436 F. Supp. 84, 89 n.4 (E.D. Tenn. 1977) ("Carried to its logical extreme, this would mean that every merchant who sells carrots to the public with knowledge that some of his consumers believe that the ingestion of carrots prevents eye diseases holds the carrots out for use as a drug, as that term is defined in the Act."), *vacated on other grounds*, 627 F.2d 1093 (6th Cir. 1980).

[48] *See* 15 U.S.C. § 1261(f)(2) (Federal Hazardous Substances Act) (excluding foods, drugs, and cosmetics regulated under the FDCA); *id.* at § 2052(a)(1)(H) (Consumer Product Safety Act) (excluding drugs, medical devices, cosmetics, and food regulated under the FDCA).

[49] *See* Letter from Stephen Lemberg, Ass't Gen. Counsel, CPSC to Mr. Leslie Fisher, New York Dep't of Health 1 (Apr. 26, 1979), available at https://www.cpsc.gov/s3fs-public/pdfs/blk_pdf_276.pdf; *see also* 21 C.F.R. § 880.5045 (FDA medical device classification regulations for medical recirculating air cleaners). CPSC's letter followed a letter from the FDA Chief Counsel, stating, "The unsatisfactory result of this analysis is that some electrostatic air cleaners will be consumer products and others (indistinguishable in their physical properties) will be medical devices due to differences in labeling claims. This is the result produced by the statutes we administer. I see no proper way for FDA to expand its jurisdiction to include air cleaners that do not make medical or health-related claims because, in the absence of such claims, it cannot be said that such products 'are intended for' any of the uses

something other than claims, the division of responsibility over many articles like air cleaners would suddenly become unclear.

Defining intended use based on a manufacturer's specific promotional claims would enable FDA to rely upon external representations by a manufacturer about the safety or efficacy of its product. This would not unduly restrict FDA's authority. A manufacturer may, and often does, sell its products through various means as part of an overall distribution and sales program, including through digital channels and other non-traditional or innovative media. The cases make clear that FDA is permitted to premise a finding of intended use on a variety of different sources of promotional claims in labeling, advertising, and analogous oral statements,[50] and that the agency is not limited to claims made on the product's label itself. The case law is consistent with the legislative history, which also focuses on specific promotional claims.[51] The claims-based interpretation is therefore sufficiently broad to permit FDA to invoke its regulatory authorities and require manufacturers to demonstrate the safety and effectiveness of their products as a condition of marketing.

III. FDA's "Loophole" Argument Is Unfounded

In the March 20 notice, FDA asserted that "evidence of intended use has been derived from sources other than explicit promotional claims" where firms have "attempt[ed] to evade FDA's medical product regulation by making no claims, or at least no explicit claims, about their products."[52] In particular, FDA cited cases in which persons distributed, including by offering for import, "substances which are known to be used recreationally to get high," "synthetic drugs, such as synthetic marijuana, labeled as incense, potpourri, or bath salts, and/or bearing the statement 'not for human consumption,'" "imitation drugs claimed to be incense or dietary supplements," and "products containing the active ingredients in prescription drugs."[53] FDA

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that make a product a medical device." Letter from Richard M. Cooper, Chief Counsel to Stephen Lemberg, Esq., Ass't Gen. Counsel, CPSC 2 (May 14, 1979), available at https://www.cpsc.gov/s3fs-public/pdfs/blk_pdf_276.pdf.

[50] In prior submissions to FDA, the MIWG has requested that the agency properly construe the terms "advertising" and "labeling" in accordance with constitutional and statutory limitations. *See, e.g.*, MIWG, White Paper: Systemic, Societal, and Legal Developments Require Changes to FDA's Regulation of Manufacturer Speech, Docket No. FDA-2013-P-1079 (Oct. 31, 2014); MIWG, Citizen Petition, Docket No. FDA-2013-P-1079 (Sept. 3, 2013). It remains vital that FDA appropriately constrain these terms so that manufacturers may reliably discern in advance whether their truthful, non-misleading communications about medical products are subject to FDA regulation.

[51] S. Rep. No. 74-361, at 4 (1935) (whether a product is a drug or device is determined by the manufacturer's "representations in connection with . . . sale" of the product); Foods, Drugs, and Cosmetics: Hearings on S. 2800 Before the Senate Comm. on Commerce, 73rd Cong. 517-18 (1934) (statement of W.G. Campbell) (the categorization of a product as a "drug"—and FDA's authority to regulate it as such—hinged on the manufacturer's representations to the public). Courts consider this legislative history authoritative. *Action on Smoking and Health v. Harris*, 655 F.2d 236, 239 (D.C. Cir. 1980); *United States v. Article . . . Sudden Change*, 409 F.2d 734, 739 n.3 (2d Cir. 1969); *Am. Health Prods. Co.*, 574 F. Supp. at 1506.

[52] 82 Fed. Reg. at 14,321.

[53] *Id.* at 14,321-22.

also cited "[o]ther instances where a person's claims about the intended use of a product are belied by the person's activities or non-promotional statements or by circumstantial evidence."[54]

The examples in the March 20 notice do not support a "totality of the evidence" standard. As a threshold matter, many of the examples clearly *did* involve promotional claims. In *United States v. Livdahl*, for example, the court found that the products at issue were "drugs" under the FDCA because the defendant made specific promotional claims, including, for example, by promoting the product "as a cheap alternative to Allergan's Botox Cosmetic at workshops they conducted."[55] As another example, in *United States v. 789 Cases, More or Less, of Latex Surgeons' Gloves, an Article of Device*, the district court based its finding on the fact that the manufacturer had inaccurately "represented [to its customer the government] that its gloves were to be used as surgeons gloves or as dental examination gloves."[56] Many of the other cases cited by FDA also focused on promotional claims,[57] and the March 20 notice provides no explanation of how an expansive definition of intended use was essential to prosecution of any of the others.

Moreover, FDA need not rely on an expanded definition of intended use to assert its authority in the situations described. FDA is able to proceed under the statutory prohibition on adulteration of food in scenarios involving products that are marketed without "drug" claims and labeled as dietary supplements, but contain synthetic drugs, imitation drugs, or active prescription drug ingredients. FDA may also proceed under the prohibition on misbranding of food if a product contains ingredients that are not declared in labeling or bear misleading claims, such as "all natural."[58] The FDCA also enables FDA to take decisive action with respect to

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[54] *Id.* at 14,322.

[55] 459 F. Supp. 2d 1255, 1260 (S.D. Fla. 2005).

[56] 799 F. Supp. 1275, 1280 (D. Puerto Rico 1992).

[57] *See United States v. Bowen*, No. 14-169, Rule 11(c)(1)(A) and (B) Plea Agreement and Statement of Facts Relevant to Sentencing 30 (D. Colo. Jan. 29, 2015) (marijuana substitute that was "marketed, distributed, and sold to consumers as a smoke product"); *United States v. Storage Spaces Designated Nos. "8" and "49,"* 777 F.2d 1363, 13666 (9th Cir. 1985) (leaflets stating that the product advertised was synthetic cocaine, product names suggesting that the products were similar or related to cocaine, and labeling with the words, "if ingested or inhaled, may cause stimulation"); *United States v. Undetermined Quantities of . . . Street Drug Alternatives*, 145 F. Supp. 2d 692, 699 (D. Md. 2001) (product names and explicit statements that, according to the court, referred to a "mind altering affect [sic] on the user"); *United States v. Zeyid*, No. 14-197, First Superseding Indictment at 3 and *passim* (N.D. Ga. June 24, 2014) (product names referring to male sexual enhancement, such as "Rock Hard Weekend" and "Stiff Nights"); *United States v. An Article of Device Toftness Radiation Detector*, 731 F.2d 1253, 1257 (7th Cir. 1984) (instructions for use in making chiropractic adjustments). Whether the claims in the cited cases would constitute therapeutic claims that would subject the articles to drug regulation under Section 201(g) of the FDCA is a separate inquiry.

[58] *See, e.g.*, 21 U.S.C. § 342(a) (prohibiting food that bears or contains any poisonous or deleterious substance); *id.* at § 343(a) (prohibiting labeling of food that is false or misleading in any particular). In 2010, FDA launched an initiative to "address[] the significant public health problems posed by products that are marketed as dietary supplements but that contain the same active ingredients as FDA-approved drugs, analogs of the active ingredients in FDA-approved drugs, or other compounds, such as novel synthetic steroids, that do not qualify as dietary ingredients." *See* Letter from Margaret A. Hamburg, M.D., Commissioner of Food and Drugs, To Manufacturers of Dietary Supplements (Dec. 15, 2010). In connection with that initiative, FDA notified manufacturers that dietary

dietary supplements and bulk dietary ingredients that contain substances that are new dietary ingredients for which there is inadequate information to provide reasonable assurance of safety within the meaning of Section 402(f)(1)(B).[59]

Other agencies, such as the Drug Enforcement Agency (DEA), would also have authority to proceed in many of the scenarios identified by FDA. Specifically, DEA has authority under the Controlled Substances Act (CSA) to pursue enforcement against illegal street drugs, including synthetic or imitation drugs that are analogues to controlled substances.[60] It also has authority under the FDCA to pursue enforcement against distribution of human growth hormone for non-therapeutic uses.[61] Indeed, the government successfully pursued charges under the CSA, and myriad other statutes, in many of the specific cases cited by FDA.[62] State governments also have a significant law enforcement role with respect to synthetic drugs, including many of those identified in the March 20 notice.[63]

Finally, the March 20 notice states that it is "common" for FDA to "evaluate materials such as research protocols in determining whether studies of products that are marketed as dietary supplements, conventional foods, or cosmetics are evaluating such products for use as drugs and are therefore subject to the investigational new drug application [(IND)] requirements under 21 C.F.R. part 312."[64] FDA's assertion that the "totality" standard is necessary to facilitate the agency's enforcement of the IND rules is incorrect. The relevant passage in the March 20 notice is derived from a guidance document that FDA first issued in draft form in

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supplements that contain active pharmaceutical ingredients are illegal, citing both the drug and the dietary supplement provisions of the statute. *Id.* at 1.

[59] 21 U.S.C. § 342(f)(1)(B). *See, e.g.,* Detention without Physical Examination of Dietary Supplements and Bulk Dietary Ingredients That Are or Contain Mitragyna Speciosa or Kratom, Import Alert 54-15 (Dec. 20, 2016).

[60] 21 U.S.C. §§ 802(32), 813, 841.

[61] *Id.* § 333(e).

[62] *See United States v. Carlson*, 810 F.3d 544 (2016) (violations of the CSA, the Controlled Substance Analogue Enforcement Act, and 18 U.S.C. § 1957 (money laundering)); *United States v. Bowen*, No. 14-169, Rule 11(c)(1)(A) and (B) Plea Agreement and Statement of Facts Relevant to Sentencing (D. Colo. Jan. 29, 2015) (violations of the CSA and 18 U.S.C. § 1957 (money laundering)); *United States v. Livdahl*, 459 F. Supp. 2d 1255 (S.D. Fla. 2005) (wire fraud, mail fraud, and perjury).

[63] *See, e.g., Synthetic Drugs, Real Danger*, Hearing Before the Subcomm. On Crime, Terrorism, Homeland Security, and Investigations of the Comm. on the Judiciary, H. R. Rep. No. 114-66 (2016), at 18 ("All 50 states have outlawed synthetic drugs in some way.") (testimony of William Smith, Jr., Fraternal Order of Police). In cases such as those involving steroids in products marketed as dietary supplements, FDA has been able to pursue both criminal and civil proceedings against unscrupulous sellers without relying on an expansive definition of intended use. *See, e.g., Body Building Products and Hidden Steroids: Enforcement Barriers*, Hearing Before the Subcomm. On Crime and Drugs of the Comm. on the Judiciary, Serial No. J-111-51 (2009), at 7-8 (statement of Michael Levy, Esq., Dir., Div. of New Drugs and Labeling Compliance, CDER).

[64] 82 Fed. Reg. at 14,322.

2010. When the guidance was finalized in 2013, it stated, for example, that an IND would be required for a study of a cosmetic product or ingredient that "is being studied for use to affect the structure or function of the body or to prevent, treat, mitigate, cure, or diagnose a disease . . . even if the study is intended to support a cosmetic claim about the ingredient or product's ability to cleanse, beautify, promote attractiveness, or alter the appearance, rather than a structure/function claim."[65] In other words, the guidance document purported to require the submission of an IND based on whether *the clinical investigation* is intended for a particular purpose. Accordingly, FDA's IND discussion in the March 20 notice is not pertinent to the scope of intended use in 21 C.F.R. §§ 201.128 and 801.4 because the guidance does not address intended use within the meaning of 21 C.F.R. §§ 201.128 & 801.4.[66]

IV. Conclusion

The Final Rule would encompass, according to the accompanying preamble, an extraordinarily broad range of potential evidentiary sources, including many types of manufacturer communication that FDA has said are not "relevant to intended use." Consequently, the Final Rule would undermine existing FDA safe harbors that specifically authorize certain forms of off-label communication to promote patient care and the public health. The Final Rule also would exacerbate the First Amendment and Fifth Amendment deficiencies of the FDA's regulatory regime because it implies that constitutionally protected speech could be treated as evidence of a new intended use.

FDA has still not completed the "comprehensive review" it committed to undertake regarding the extent to which the First Amendment constrains FDA's authority to restrict manufacturer speech. Moreover, the Final Rule does not provide the clarity required by the Fifth Amendment, because it does not clearly define what speech may serve as evidence of intended use and does not clearly exclude speech covered by longstanding FDA safe harbors.

The approach taken by FDA in the Final Rule is also deeply flawed because the "totality" standard conflicts with the relevant legislative history, the case law, and the statute. Moreover, a broad interpretation of intended use is *not* necessary to address situations in which products are sold by a firm that "attempt[s] to evade FDA's medical product regulation by making no claims,

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[65] FDA, Guidance for Clinical Investigators, Sponsors, and IRBs: Investigational New Drug Applications (INDs)—Determining Whether Human Research Studies Can Be Conducted Without an IND, 11 (Sept. 2013); *see also id.* at 12, 13 (an IND is required if a study is "intended to evaluate" a dietary supplement or conventional food for its ability to diagnose, cure, mitigate, treat, or prevent disease).

[66] *Id.* at 11, 12, and 13 (noting, for example, that "a dietary supplement is not considered a drug and is not subject to the premarket approval requirements for drugs if the intended use for which it is marketed is only to affect the structure or any function of the body (i.e., not intended to be used for a therapeutic purpose)," but "whether an IND is needed for a clinical investigation evaluating a dietary supplement is determined by the intent of the clinical investigation"); *see also* 82 Fed. Reg. at 14,322 (reflecting the same distinction by acknowledging that FDA evaluates "the purpose of the research" in determining whether a dietary supplement, conventional food, or cosmetic "should be considered a drug" *solely* "for the purpose of the investigation").

or at least no explicit claims, about their products."[67] In such cases, FDA and other federal agencies, including particularly DEA, would have broad statutory authority to take immediate and forceful action to protect the public health—and the legal tools available to the government in those cases would not require FDA to adopt a tortured statutory interpretation that would create significant dislocations in other areas.

In sum, FDA's "totality" theory would undermine the agency's own long-standing public health policy decisions, conflict with the applicable legal authorities, and present significant constitutional issues. And it is not necessary to adopt such a controversial and unsupported approach to permit FDA to address the specific scenarios set forth in the preamble. For the reasons discussed above, FDA should remove from the Final Rule (1) the "totality" language, (2) the last sentence relating to "knowledge," as originally provided in the Proposed Rule, (3) the reference to "circumstances surrounding distribution," and (4) any other language that suggests FDA may define intended use based on evidence other than promotional claims.

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[67] 82 Fed. Reg. at 14,321.