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November 14, 2017

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

Re: Regulatory Considerations for Microneedling Devices; Draft Guidance for Industry and Food and Drug Administration Staff; Availability (Docket No. FDA-2017-D-4792)

The Medical Information Working Group (MIWG) submits these comments in response to FDA's September 15, 2017 notice (82 Fed. Reg. 43,383) inviting comments on FDA's Draft Guidance for Industry and Food and Drug Administration Staff: Regulatory Considerations for Microneedling Devices (Microneedling Draft Guidance). 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 drugs and medical devices and new uses of lawfully marketed products.[1]

The Microneedling Draft Guidance interprets intended use in a manner that conflicts with federal law, which is grounded in the principle that intended use is determined by a manufacturer's promotional claims.[2] In particular, the Microneedling Draft Guidance advances an interpretation of intended use that would permit consideration of a wide variety of evidence, including but not limited to product design and technological characteristics and features, to determine intended use.[3]

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[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] *See, e.g.*, MIWG, Comments on "Intended Use" Final Rule, Docket No. FDA-2015-N-2002-2001 (July 18, 2017); MIWG, PhRMA & Bio, Petition to Stay and for Reconsideration, Docket No. FDA-2015-N-2002-1977 (Feb. 8, 2017). MIWG is cross-filing these comments on the Microneedling Draft Guidance to the intended use comments docket, Docket No. FDA-2015-N-2002.

[3] *See, e.g.*, Microneedling Draft Guidance, at 8.

The MIWG has previously expressed its concerns with any interpretation of intended use that would allow FDA to consider evidence other than a manufacturer's promotional claims.[4] On January 9, 2017, FDA issued a final rule that would significantly modify the regulatory definitions of intended use for drugs and medical devices by, *inter alia*, incorporating a "totality of the evidence" standard.[5] On February 8, 2017, the MIWG, the Pharmaceutical Research and Manufacturers of America (PhRMA), and the Biotechnology Innovation Organization (BIO) submitted a Petition to Stay and for Reconsideration of this final rule. On March 20, 2017, in effectively granting the MIWG's Petition, FDA published a Federal Register notice announcing a delayed effective date of the final rule until March 19, 2018, and soliciting public comments regarding various issues relating to intended use.[6] On July 18, 2017, the MIWG submitted comments in response to the March 20 notice.

The Microneedling Draft Guidance uses the same non-claims approach to intended use that is the subject of the ongoing rulemaking, improperly preempts that rulemaking, and is unlawful for the reasons the MIWG has described in prior submissions. We request that the agency refrain from adopting legal or policy positions on intended use outside of the intended use rulemaking and request that FDA remove any language from the Microneedling Draft Guidance suggesting that the agency can determine the intended use of a product based on evidence other than a manufacturer's promotional claims.

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[4] *See, e.g.*, MIWG, Comments on "Intended Use" Final Rule, Docket No. FDA-2015-N-2002-2001 (July 18, 2017); MIWG, PhRMA & Bio, Petition to Stay and for Reconsideration, Docket No. FDA-2015-N-2002-1977 (Feb. 8, 2017). These submissions are attached as Attachments A and B, respectively, hereto.

[5] 82 Fed. Reg. 2,193 (Jan. 9, 2017).

[6] 82 Fed. Reg. 14,319 (Mar. 20, 2017).

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Attachments

Attachment A

SIDLEY AUSTIN LLP
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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.

Respectfully submitted,

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

Attachment B

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February 8, 2017

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PETITION TO STAY AND FOR RECONSIDERATION

On behalf of the Medical Information Working Group (MIWG), the Pharmaceutical Research and Manufacturers of America (PhRMA), and the Biotechnology Innovation Organization (BIO), we respectfully submit the following Petition to Stay and for Reconsideration (Petition).

I. Decision Involved

This Petition challenges the final rule entitled *Clarification of When Products Made or Derived From Tobacco Are Regulated As Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses"* (Final Rule), which was published in the Federal Register on January 9, 2017.[1] In particular, this Petition challenges the amendments that the Final Rule would make to Food and Drug Administration (FDA) regulations defining the legal concept of "intended use."[2]

II. Actions Requested

A. Pursuant to 21 C.F.R. § 10.35(b), the MIWG respectfully requests that the Commissioner of Food and Drugs (Commissioner) indefinitely stay the Final Rule.

B. Pursuant to 21 C.F.R. § 10.33(b), the MIWG respectfully requests that the Commissioner reconsider the Final Rule and direct FDA staff to promulgate final definitions of intended use that are consistent with the proposed definitions set out in the notice of proposed rulemaking dated September 25, 2015.[3]

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[1] *See* 82 Fed. Reg. 2193, 2217 (Jan. 9, 2017).

[2] *See* 21 C.F.R. §§ 201.128, 801.4.

[3] *See* 80 Fed. Reg. 57756, 57764-65 (Sept. 25, 2015).

III. Statement of Grounds

A. Background

This Petition arises out of FDA's unexpected decision in January 2017 to revise the definitions of "intended use" for drugs and medical devices in 21 C.F.R. §§ 201.128 and 801.4 to include a new "totality of the evidence" standard. FDA's revisions were not communicated to the public prior to the Final Rule published on January 9, 2017, which deprived stakeholders of fair notice and an opportunity to be heard in violation of the Administrative Procedure Act (APA). Moreover, if allowed to take effect, the revisions would run contrary to the settled interpretation of both the statutory definitions that turn on "intended use" in the Federal Food, Drug, and Cosmetic Act (FDCA) and the requirement that drug and device labeling include "adequate directions for use."

1. Intended Use Under The FDCA

The "intended use" of a product is a core operational principle around which the FDCA is organized.[4] The concept of an intended use has its origins in the Pure Food and Drugs Act (1906 Act), which had defined the term "drug" to include both those drugs listed in the official compendia and any other "substance or mixture of substances *intended to be used* for the cure, mitigation, or prevention of disease."[5] Through this definition Congress ensured that the labeling and purity requirements of the 1906 Act would not be "confine[d] . . . to any definition of 'drug' found in dictionaries or pharmacopoeias."[6] Congress was specifically concerned to ensure that the law apply to "proprietary" medications that were not listed in any compendia but were marketed subject to claims of therapeutic value.[7]

From the outset, the "intended use" prong of the drug definition related to the manufacturer's claims for its products. Mundane articles were deemed drugs when marketed with therapeutic claims,[8] and when manufacturers sought to claim the benefit of drug status for

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[4] *See, e.g.*, 21 U.S.C. § 321(g)(1)(B)-(D) (defining drugs); *id.* § 321(h)(2)-(3) (defining devices); *id.* § 321(i)(1)-(2) (defining cosmetics); *id.* § 321(s) (defining food additives); *id.* § 321(w) (defining animal feed); *id.* § 321(ff)(1) (defining dietary supplements); *id.* § 321(rr) (defining tobacco products).

[5] Ch. 3915, § 6, 34 Stat. 768, 769 (June 30, 1906) (emphasis added).

[6] *Bradley v. United States*, 264 F. 79, 81 (5th Cir. 1920).

[7] *See Hearing on H.R. 3109 before the S. Comm. on Manufactures*, 57th Cong., 4 (Jan. 20, 1903); *see generally Hearings on S. 198 Before the S. Comm. on Manufactures*, 58th Cong. (Jan. 6, 1904).

[8] *See, e.g.*, *Bradley*, 264 F. at 80 (water deemed to be a drug when marketed with therapeutic claims); *Goodwin v. United States*, 2 F.2d 200, 200 (6th Cir. 1924) (same).

their products,[9] they were often unsuccessful unless they could show that their products had been marketed with therapeutic claims.[10]

When the FDCA was enacted in 1938, its sponsors made clear that intended use would turn on representations by the manufacturer.[11] 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.[12]

As another example, "soaps sold only for ordinary toilet or household use . . . [would] not be subject to the definition of drug, [but] soaps for which claims concerning disease are made or which are sold as pharmacopoeial articles will come within the definition of drug and will thus be subject to regulation."[13]

Courts have treated this legislative history as authoritative. For instance, in *United States v. 46 Cartons . . . Fairfax Cigarettes*, the district court relied on it to hold that cigarettes marketed with therapeutic claims were properly categorized as drugs.[14] In *United States v.*

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[9] At the time, drugs were frequently subject to less stringent regulation than other classes of products. *See, e.g.*, Peter Barton Hutt, *Government Regulation of Health Claims in Food Labeling and Advertising* 41 Food and Drug L.J. 3, 5 n.8 (1986) ("Because food misbranding could be proved merely by showing a 'misleading' statement, it was more difficult for FDA to win a drug misbranding case than a food misbranding case.").

[10] *See, e.g.*, Jury Instructions, *United States v. Four Boxes of Mulford's Wintergreens* (N.D.N.Y. 1914) ("Now, gentleman, wintergreen they tell you is a drug. A stick of wintergreen candy which you buy for your child you would hardly call a drug. . . . However, gentlemen, . . . if that was the purpose in its manufacture and sale, even though a large amount of sugar and but a trifle of this essence or oil it, why, then, of course, it would at once . . . take its place in the category of drugs"), *reprinted in* Otis H. Gates, *Decisions of Courts in Cases under the Federal Food and Drugs Act*, 593 (1934); *see also Savage v. Scovell*, 171 F. 566, 567 (E.D. Ky. 1908) ("Plaintiff is in no position to complain of his article being treated as what he calls it."); *Commonwealth v. Marzynski*, 21 N.E. 228, 229 (Mass. 1889) "[T]here was no evidence in the present case that the cigars which the defendant sold were used, *or were intended to be used*, as a medicine.") (emphasis added).

[11] *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").

[12] S. Rep. 493, 73d Cong. 2d Sess., 3 (Mar. 15, 1934); S. Rep. 361, 74th Cong., 1st Sess., 4 (1935) (same).

[13] S. Rep. 361, 74th Cong., 1st Sess., at 3-4.

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

Article of 216 Cartoned Bottles, "Sudden Change," the Second Circuit relied on the same history to hold that a cosmetic lotion was a drug because "labeling and promotional claims show intended uses that bring it within the drug definition."[15] In *NNFA v. FDA*, the Second Circuit relied on the legislative history to conclude that FDA had erred in attempting to regulate vitamins as drugs in the absence of therapeutic claims.[16] In *ASH v. Harris*, the D.C. Circuit relied on this legislative history when it upheld FDA's decision that cigarettes were not medical products in the absence of therapeutic claims.[17] The D.C. Circuit found that the claims-based understanding of intended use had been accepted "as a matter of statutory interpretation."[18] In other words, courts "*have always* read . . . the statutory definitions employing the term 'intended' to refer to specific marketing representations."[19] The Fourth Circuit subsequently observed—twice—that "*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."[20] Indeed, in 2002 and again in 2004, FDA itself echoed that conclusion.[21]

2. FDA's Intended Use Definition

As described above, section 502(f)(1) of the FDCA states that a drug or device is misbranded unless its labeling "bears adequate directions for use."[22] Although Congress amended section 503(b)(2) of the FDCA in 1951 to provide that 502(f)(1) does not apply to prescription drugs,[23] FDA promulgated a regulation in 1952 that purported to exempt prescription drugs from section 502(f)(1) only if, among other things, the prescription drug's labeling contains "adequate information" regarding any "use for which [the drug] is intended."[24] The 1952 regulation also created the first ever regulatory definition of intended use. According to FDA:

> The words "intended uses" or words of similar import . . . refer to the objective intent of the persons legally responsible for the labeling of

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[15] *United States v. Article of 216 Cartoned Bottles, "Sudden Change,"* 409 F.2d 734, 736, 739 & n.3 (2d Cir. 1969).

[16] *NNFA v. FDA*, 504 F.2d 761, 789 & n.35 (2d. Cir. 1974).

[17] *ASH v. Harris*, 655 F.2d 236, 238-39 (D.C. Cir. 1980).

[18] *Id.* at 239.

[19] *American Health Products Co., Inc. v. Hayes*, 574 F. Supp. 1498, 1505 (S.D.N.Y. 1983) (emphasis added).

[20] *Sigma-Tau Pharms., Inc. v. Schwetz*, 288 F.3d 141, 146-47 (4th Cir. 2002) (emphasis added); *Brown & Williamson Tobacco Corp. v. FDA*, 153 F.3d 155, 163 (4th Cir. 1998) (same), *aff'd* 529 U.S. 120 (2000).

[21] *See* Letter from Daniel E. Troy, Chief Counsel, FDA to Jeffrey N. Gibbs, Esq., 3 (Oct. 17, 2002); Citizen Petition Response, Docket No. 2003P-0321, 23-24 (Apr. 6, 2004) (Ribavirin Petition Response).

[22] *See* 21 U.S.C. § 352(f)(1).

[23] *See id.* § 353(b)(2).

[24] 21 C.F.R. § 201.100(c)(1).

> drugs and devices. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. It may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised. The intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer. If, for example, a packer, distributor, or seller intends an article for different uses than those intended by the person from whom he received the drug, such packer, distributor, or seller is required to supply adequate labeling in accordance with the new intended uses. *But if a manufacturer knows, or has knowledge of facts that would give him notice, that a drug or device introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a drug which accords with such other uses to which the article is to be put.*[25]

The above definition of intended use became codified at 21 C.F.R. § 201.128 (for drugs) and at 21 C.F.R. § 801.4 (for medical devices) where it remained in place without substantive revision until the events at issue in this Petition.[26]

FDA's intended use definition has always been problematic, particularly the last sentence regarding a manufacturer's knowledge of actual uses and the corresponding obligation to "provide adequate labeling." Manufacturers specifically objected in 1952 to the possibility that misbranding liability could be based on a known, but not manufacturer-recommended, use. They objected, as well, to any obligation to provide labeling regarding such a use.[27]

Courts also have questioned FDA's intended use definition. In 1998, FDA published a rule purporting to require manufacturers of approved drugs "to provide adequate labeling" regarding the use of their products in children, even if pediatric use was neither claimed nor

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[25] *Id.* § 1.106(o) (1955 ed.) (emphasis added).

[26] *See* 40 Fed. Reg. 13996 (Mar. 27, 1975); 41 Fed. Reg. 6896 (Feb. 13, 1976).

[27] *See, e.g.*, Letter from John L. Hammer, Vice President, Smith, Kline & French Labs. to Hearing Clerk, Federal Security Agency (Mar. 4, 1952) (objecting that, under the new intended use regulation, if a manufacturer's "market research department learns that 20% of the purchasers use the preparation as a sedative . . . [and] he inserts in his label directions for use as a sedative . . . he is forced into the position of recommending his product for a use of which he heartily disapproves and for which his drug may be largely ineffective").

recommended.[28] Citing 21 C.F.R. § 201.128, FDA contended that an approved drug's intended uses include "the actual uses of the drug of which the manufacturer has, or should have, notice, even if those uses are not promoted by the manufacturer."[29] That reasoning was rejected by the court in *Association of American Physicians and Surgeons, Inc. v. FDA*, which ruled that FDA "may only regulate claimed uses of drugs, not all foreseeable or actual uses."[30] The court found the agency's reliance on 21 C.F.R. § 201.128 particularly unavailing because "'no order or regulation issued by an administrative agency can confer on it any greater authority than it has under the statute.'"[31]

More recently, medical product manufacturers have challenged FDA's intended use definition as an unconstitutional restraint on protected speech regarding unapproved uses of approved medical products. A lawsuit brought by Allergan, Inc. in 2009 alleged that FDA's intended use regulations had chilled speech regarding methods to minimize the risks and improve the quality of patient care related to a particular off-label use.[32] Similarly, a lawsuit brought by Par Pharmaceuticals, Inc. in 2011 alleged that the government had chilled speech by purporting to find a new, unapproved intended use based on the identity of the audience hearing the plaintiff's speech related to an approved indication.[33] FDA settled both cases before the district court could rule, but made representations in each case limiting how it would interpret and apply 21 C.F.R. § 201.128. In the *Allergan* case, FDA stated that "not all speech or actions by a manufacturer regarding an unapproved use is [sic] taken by FDA to be evidence of intended use."[34] FDA further stated that, contrary to the last sentence of 21 C.F.R. §§ 201.128 and 801.4, the agency "usually" does not rely on a manufacturer's knowledge to infer an intended use.[35] Similarly, during oral argument in *Caronia*, the court asked whether a crime is committed if a person "hasn't promoted but he sent [a drug] out knowing and perhaps intending that it be used for something other than an on-label use." The government counsel replied: "I believe not, your Honor, I don't think that would be a crime."[36]

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[28] 63 Fed. Reg. 66632 (Dec. 2, 1998).

[29] *Id.* at 66658.

[30] *Ass'n of Am., Physicians & Surgeons, Inc. v. FDA*, 226 F. Supp. 2d 204, 217-18 (D.D.C. 2002).

[31] *Id.* at 215 n.17 (quoting *Office of Consumers' Counsel v. FERC*, 655 F.2d 1132, 1149 n. 32 (D.C. Cir. 1980)).

[32] *See* Compl., *Allergan, Inc. v. United States*, No. 09-1879 Dkt. 1-2, ¶¶ 94, 132-33, 135 (D.D.C. filed Oct. 1, 2009).

[33] *See* Compl., *Par Pharm., Inc. v. United States*, No. 11-1820, Dkt. 1, ¶ 85 (D.D.C. filed Oct. 14, 2011).

[34] Def. Mem. in Support of Mot. to Dismiss or For Summary Judgment, *Allergan, Inc. v. United States*, No. 09-1879 Dkt. 18, 22 (D.D.C. filed Dec. 11, 2009).

[35] *Id.* at 22.

[36] Tr. of Oral Arg. At 10, *United States v. Caronia*, No. 09-5006 (2d Cir. Dec. 2, 2010).

3. The Rulemaking At Issue

FDA's intended use definition also has been the subject of at least two citizen petitions. First, a petition submitted in 2001 requested that FDA strike the last sentence of 21 C.F.R. § 201.128 (regarding a manufacturer's knowledge or notice of actual use) because it was inconsistent with "the general regulatory scheme for review and approval of products based on claims made by the sponsor."[37] FDA has never addressed that petition on its merits.

Second, in September 2013, the MIWG submitted a petition urging the agency to conduct a comprehensive review of its regulations in view of the limitations imposed by the Fifth and First Amendments. Among other things, the MIWG specifically requested that FDA strike the last sentence of 21 C.F.R. §§ 201.128 and 801.4 concerning knowledge.[38] In June 2014, FDA granted the MIWG's citizen petition and committed to "a comprehensive review of the regulatory regime governing communications about medical products."[39] In December 2014, FDA reiterated that taking action on the issues raised by the MIWG's petition were among FDA's "highest priorities" for 2015.[40]

a. FDA's Proposed Rule Would Have Acknowledged Key Limits on the Scope of "Intended Use."

In September 2015, FDA published a notice of proposed rulemaking that appeared to grant the relief requested by both the MIWG and the 2001 petition. FDA explained that changes to 21 C.F.R. §§ 201.128 and 801.4 were needed "to reflect how the agency currently applies them to drugs and devices."[41] Citing its own briefing from the *Allergan* case, FDA stated that it will no longer "regard a firm as intending an unapproved new use for an approved or cleared medical product based solely on that firm's knowledge that such product was being prescribed or used by doctors for such use."[42] Accordingly, FDA proposed the following alterations to the intended use definitions:

> The words intended uses or words of similar import ... refer to the objective intent of the persons legally responsible for the labeling of drugs. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims,

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[37] Citizen Petition, Docket Nos. FDA-2001-P-0521, 01P-0228, 2 (May 8, 2001).

[38] Citizen Petition, Docket No. 2013-P-1079, 4, 15-19 (Sept. 3, 2013).

[39] Citizen Petition Response, Docket Nos. FDA-2011-P-0512 and FDA-2013-P-1079, 2 (June 6, 2014).

[40] Letter from FDA re: Docket Nos. FDA-2011-P-0512 and FDA-2013-P-1079, 2 (Dec. 22, 2014).

[41] 80 Fed. Reg. at 57756.

[42] *Id.* at 57761.

> advertising matter, or oral or written statements by such persons or their representatives. It may be shown ~~by the~~, for example, by circumstances ~~that~~in which the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised. The intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer. If, for example, a packer, distributor, or seller intends an article for different uses than those intended by the person from whom he received the drug, such packer, distributor, or seller is required to supply adequate labeling in accordance with the new intended uses. ~~But if a manufacturer knows, or has knowledge of facts that would give him notice, that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a drug which accords with such other uses to which the article is to be put.~~[43]

FDA asserted that, in light of the positions taken in the *Allergan* case, the deletion of the last sentence in the intended use definition "would not reflect a change in FDA's approach regarding evidence of intended use for drugs and devices."[44] Notably, the preamble to the proposed rule included no discussion of any alternative approaches, options, or proposals regarding the intended use definition.

FDA originally provided stakeholders 60 days to submit written comments on the proposed rule, through November 24, 2015.[45] In response to a request for an extension, FDA held the docket open for comments through December 30, 2015.[46] FDA received nearly 2,000 comments on the proposal, most of which did not directly address the revisions to 21 C.F.R. §§ 201.128 and 801.4. The comments that did discuss those revisions generally lauded FDA's proposal, although some proposed additional changes to make the intended use definition more consistent with the language of the statute and/or constitutional requirements.[47] For its part, the

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[43] *See id.* at 57764-65.

[44] *Id.* at 57761.

[45] *Id.* at 57756.

[46] 80 Fed. Reg. 74737 (Nov. 30, 2015).

[47] *See, e.g.*, 510(k) Coalition, Comment to Docket. No. FDA-2015-N-2002, 1 (Nov. 23, 2015); American Association of Tissue Banks – Tissue Policy Group, Comment to Docket. No. FDA-2015-N-2002, 1 (Nov. 24, 2015); Washington Legal Foundation, Comment to Docket. No. FDA-2015-N-2002, 10 (Nov. 24, 2015); Pharmaceutical Research and Manufacturers of America, Comment to Docket. No. FDA-2015-N-2002, 1 (Nov. 24, 2015); Musculoskeletal Transplant Foundation, Comment to Docket. No. FDA-2015-N-2002, 1 (Nov. 25, 2015); AdvaMed, Comment to Docket. No. FDA-2015-N-2002, 1 (Dec. 18, 2015). One comment did object to the fact that FDA's proposal to amend 21 C.F.R. §§ 201.128 and 801.4 had been "buried" in what was "primarily a Tobacco rule making docket." *See* Jason Williams, Comment to Docket No. FDA-2015-N-2002 (Mar. 2, 2016).

MIWG understood that FDA's proposal to strike the last sentence of sections 201.128 and 801.4 was part of FDA's effort to take action on the MIWG's 2013 petition, which had been granted in June 2014.[48]

After proposing to strike the last sentence of the old intended use definition, FDA finally took administrative action on the 2001 citizen petition. As discussed, that petition had requested precisely the same relief as was proposed by FDA in the September 2015 notice.[49] Just before the deadline for comments on that proposal, FDA sent a letter to the successor of the law firm that had filed the 2001 citizen petition. FDA's letter stated that "the petition ha[d] been inactive for many years" and suggested that the petition had become moot in light of the proposed rule.[50] Two months later, after the comment period had closed, FDA unilaterally deemed the 2001 petition to have been withdrawn.[51]

b. The Final Rule Unexpectedly Expanded the Understanding of Intended Use.

On January 9, 2017, however, FDA dramatically shifted gears. Rather than delete the final sentence of the intended use definition, the agency replaced it with an entirely new sentence that created an open-ended "totality of the evidence" standard:

> ~~But if~~And if the totality of the evidence establishes that a manufacturer ~~knows, or has knowledge of facts that would give him notice,~~objectively intends that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than ~~the~~ ones for which ~~he offers~~ it is approved (if any), he is required ~~to provide~~, in accordance with section 502(f) of the Federal Food, Drug, and Cosmetic Act, or, as applicable, duly promulgated regulations exempting the drug from the requirements of section 502(f)(1), to provide for such drug adequate labeling ~~for such a drug which~~that accords with such other intended uses ~~to which the article is to be put~~.[52]

The Final Rule did not claim that this "totality of the evidence" standard had been mentioned as part of the proposed rulemaking. Nor did the Final Rule claim that the new "totality" standard

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[48] *See* MIWG, Comments to Docket No. FDA-2015-N-2002, 1 (Nov. 24, 2015). The MIWG also explained that, contrary to FDA's position, ongoing government investigations continued to assert that intended use could be shown through knowledge of actual use. *See id.* at 2.

[49] Citizen Petition, Docket Nos. FDA-2001-P-0521, 01P-0228, 2 (May 8, 2001).

[50] Letter from Nan Kim, FDA to Terry S. Coleman, Ropes & Gray (Dec. 22, 2015).

[51] Memorandum from Office of Regulatory Policy, FDA to Division of Dockets Management, FDA re: Docket No. FDA-2001-P-0521 (Feb. 1, 2016).

[52] 82 Fed. Reg. at 2217.

had been proposed by any of the numerous comments submitted. Instead, FDA claimed that certain, unidentified comments had "misunderstood FDA's proposal" to delete the last sentence of sections 201.128 and 801.4.[53] FDA claimed that it had sought in the proposed rule to clarify that knowledge of an actual use did not "automatically trigger obligations for the manufacturer to provide labeling," but had not meant to suggest that knowledge would be "eliminate[d] . . . altogether as a source of evidence of intended use."[54] FDA therefore concluded that its goals would "be better achieved by amending the last sentence of each regulation, rather than deleting them."[55]

B. Argument

The Final Rule published on January 9, 2017 should be stayed indefinitely and reconsidered for two independent reasons. *First*, the Final Rule was promulgated in violation of the APA because it failed to give parties subject to potentially significant and far-reaching liability fair notice or a meaningful opportunity to comment. *Second*, while the agency claims that the Final Rule was merely a clarification of law, it in fact adopted a new "totality of the evidence" standard for finding an intended use that is not found in the FDCA or the case law addressing the intended use question.

1. The Final Rule Violated The Fair Notice Requirements of the Administrative Procedure Act.

The notice-and-comment provisions of the APA "are designed (1) to ensure that agency regulations are tested via exposure to diverse public comment, (2) to ensure fairness to affected parties, and (3) to give affected parties an opportunity to develop evidence in the record to support their objections to the rule and thereby enhance the quality of judicial review."[56] To fulfill these goals, an agency must "make its views known to the public in a concrete and focused form so as to make criticism or formulation of alternatives possible."[57] The agency must "describe the range of alternatives being considered with reasonable specificity,"[58] and "set out [the agency's] thinking," so that parties can respond with an "adversarial critique of the agency."[59] Thus, although a final rule need not be identical to the proposed rule,[60] the two "may

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[53] *Id.* at 2205.

[54] *Id.* at 2206.

[55] *Id.*

[56] *Int'l Union, United Mine Workers of Am. v. Mine Safety & Health Admin.*, 407 F.3d 1250, 1259 (D.C. Cir. 2005).

[57] *HBO, Inc. v. FCC*, 567 F.2d 9, 36 (D.C. Cir. 1977).

[58] *Small Refiner Lead Phase-Down Task Force v. EPA*, 705 F.2d 506, 549 (D.C. Cir. 1983).

[59] *HBO*, 567 F.2d at 36, 55.

[60] *Small Refiner*, 705 F.2d at 546.

differ only insofar as the latter is a 'logical outgrowth' of the former."[61] If the agency wishes to pursue an alternative that is not a logical outgrowth of the original proposed rule, the agency must provide a supplemental notice of proposed rulemaking and provide an additional opportunity for comment.[62]

As to the intended use definitions in 21 C.F.R. §§ 201.128 and 801.4, the Final Rule was a stark reversal of the proposed rule and, therefore, violated the APA's notice-and-comment provisions. While the proposed rule would have helped to address substantial concerns regarding FDA's intended use definitions, the Final Rule instead exacerbates those concerns. As discussed, regulated entities have long argued that it is inappropriate to impose liability based solely on knowledge of actual use. Industry representatives have requested revisions to FDA's intended use regulations in comments dating back to 1952 and also filed formal citizen petitions requesting that FDA reconsider its approach. The 2015 proposed rule appeared to be responsive to those concerns by striking the final sentence of the intended use regulations entirely.

Deleting the last sentence from 21 C.F.R. §§ 201.128 and 801.4 would have altered FDA's intended use definitions in two important respects. First, it would have deleted the only *command* found in either regulation—namely, the command that manufacturers "provide adequate labeling" for known, but not recommended, uses.

Second, it would have resulted in a streamlined definition focusing on certain types of claims attributable to the manufacturer. Specifically, the proposed rule would have left three operative sentences providing that

> The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. It may be shown, for example, by circumstances in which the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised.[63]

These sentences would have limited the definition of intended use to manufacturers' "expressions" (most notably labeling and advertising) and sales and marketing activities (how the product is both "*offered* and used"). Thus, the definition in the proposed rule would have turned solely on the manufacturer's promotional statements.

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[61] *Envtl. Integrity Project v. EPA*, 425 F.3d 992, 996-97 (D.C. Cir. 2005).

[62] *See United Steelworkers of Am., AFL-CIO-CLC v. Schuylkill Metals Corp.*, 828 F.2d 314, 317-18 (5th Cir. 1987).

[63] 80 Fed. Reg. at 57764.

The Final Rule significantly altered course, changing the definition of intended use by introducing a new, and overly broad, "totality of the evidence" standard that is not found in the FDCA and allows FDA to consider any evidence, *including knowledge*. Furthermore, the Final Rule restores to the regulations the command that manufacturers provide "adequate labeling." These changes were not hinted at in FDA's proposed rule, which promised only a modest clarification to the agency's intended use regulations. The agency therefore failed to give regulated parties fair notice of a fundamental change to the regulatory scheme for drugs and devices.[64] The revisions contained within the Final Rule thus violate the fundamental principle that agencies may not "use the rulemaking process to pull a surprise switcheroo."[65]

The comments submitted on the 2015 proposed rule further demonstrate that the Final Rule violates the logical outgrowth doctrine. Although close to 2,000 comments were received on the proposed rule, the overwhelming majority pertained to the tobacco regulations covered in the proposal; only a relative few even addressed the intended use definitions applicable to drugs and medical devices. If FDA had provided medical product manufacturers with notice that it was considering retaining the command in the last sentence of 21 C.F.R. §§ 201.128 and 801.4 and expanding the definition of intended use to include a new totality of the evidence standard, then FDA "would doubtless have triggered an avalanche of comments, in contrast to the mere [handful of] pages that . . . actually" addressed intended use.[66]

For instance, if given an opportunity, stakeholders surely would have challenged FDA's decision to use a "totality" approach as an FDCA linchpin. As the Supreme Court has observed, a "totality" standard is "not a test at all but an invitation to make an ad hoc judgment."[67] The Court also previously *invalidated* a "totality" approach in the patent context on the ground that it was "unnecessarily vague" and failed to provide inventors with "a definite standard" to guide their decisions.[68] These concerns about overbreadth and vagueness take on special weight where, as here, FDA is purporting to define the scope of its own jurisdiction.[69] Indeed, the ad

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[64] That industry lacked notice of the change is clear from both these circumstances and from FDA's claim that stakeholder comments reflected confusion about the import of the proposed revision. 82 Fed. Reg. at 2205-2206 (referring to comments that "misunderstood FDA's proposal").

[65] *Envtl. Integrity Project*, 425 F.3d at 996.

[66] *Allina Health Servs. v. Sebelius*, 746 F.3d 1102, 1108 (D.C. Cir. 2014).

[67] *City of Arlington v. FCC*, 133 S. Ct. 1863, 1874 (2013); *see also ABC, Inc. v. Aereo, Inc.*, 134 S. Ct. 2498, 2517 (2014) (Scalia, J., dissenting) ("th'ol' totality-of-the-circumstances test . . . is not a test at all but merely assertion of an intent to perform test-free, ad hoc, case-by-case evaluation").

[68] *Pfaff v. Wells Elecs.*, 525 U.S. 55, 65-66 & n.11 (1988); *see also United States v. Rivera-Rodriguez*, 318 F.3d 268, 276 (1st Cir. 2003) (explaining that the Sentencing Commission had amended the guideline for a departure based on aberrant behavior to overrule the "totality of circumstances" approach adopted by the First Circuit and other courts on the ground that it was "overly broad and vague").

[69] FDA's statements in the final rule's accompanying preamble—which are binding statements of official agency policy according to the agency's own regulations, 21 C.F.R. § 10.85(k)—demonstrate the breadth of the new "totality" standard. The preamble states that FDA will define intended use based on "evidence of a manufacturer's

hoc approach endorsed in the Final Rule would allow *qui tam* relators and prosecutors to predicate claims or charges against a manufacturer on the entirely legitimate activity of accurately forecasting demand for products (which typically includes a mix of approved and unapproved uses) and then scaling production to meet that demand. Neither the statute nor the decades of case law construing it justify such a sweeping approach to the intended use inquiry.[70] Moreover, as discussed below, exposing companies to potential liability based on an ad hoc totality standard raises significant constitutional questions.

The APA requires that industry be provided notice and a meaningful opportunity to comment before the agency promulgates a regulation with such profound consequences. The proposed rule did not provide such notice. The proper recourse to remedy this absence of notice is for the agency to stay the Final Rule and promulgate a revised rule consistent with the notice of proposed rulemaking published in September 2015.

2. "Totality Of The Evidence" Is A New And Unjustified Legal Standard.

In the preamble to the Final Rule, FDA argues that the new "totality of the evidence" standard has "solid support" in the law because courts allegedly have allowed FDA to consider "any relevant source" of evidence, including "a variety of direct and circumstantial evidence" such as the "circumstances surrounding the manufacture and distribution of a medical product."[71] FDA further asserts that the "totality" standard is inconsequential and does not reflect a change in the law or in the agency's practices.[72] These arguments lack merit. There is no support in existing law for the totality standard, and it would represent a substantial change with significant constitutional and public health ramifications.

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marketing plans," 82 Fed. Reg. 2207, "evidence of a manufacturer's . . . directions to its sales force," *id.* at 2207, 2208, "evidence of the well-known uses and abuses of its products," *id.* at 2207, "circumstantial evidence relating to the sale and distribution of the product," *id.*, evidence that a product "contain[s] a pharmacological ingredient," *id.* at 2208, "internal firm documents and circumstances surrounding the sale of products," *id.*, "consumer intent," *id.*, evidence of claims that were never communicated to the public, *id.*, and the "overall circumstances." *Id.*

[70] *Cf. Nat'l Nutritional Foods Ass'n (NNFA) v. Mathews*, 557 F.2d 325, 334-35 (2d Cir. 1977) ("The determination that an article is properly regulated as a drug [or device] is not left to the Commissioner's unbridled discretion to act to protect the public health but must be in accordance with the statutory definition[s]."); *Health Prods. Co. v. Hayes*, 574 F. Supp. 1498, 1507 (S.D.N.Y. 1983) ("[A] court's responsibility to construe the [FDCA] in accord with its protective purposes does not confer a license to ignore congressional judgments reflected in the classification scheme."), *aff'd on other grounds*, 744 F.2d 912 (2d Cir. 1984).

[71] *See* 82 Fed. Reg. at 2206; *see also id.* at 2195-96, 2199, 2202, 2208.

[72] *See, e.g., id.* at 2204.

a. The totality standard has no basis in existing law.

FDA's claim that the totality standard is a mere clarification that tracks existing law is incorrect. The FDCA does not contain the phrase "totality of the evidence," and the courts have not endorsed that approach to intended use. Moreover, the first and only FDA document to assert that intended use should be assessed according to a "totality" standard appears to be a final guidance published in November 2013 regarding *in vitro* diagnostic (IVD) products.[73] The draft IVD guidance published in 2011 was highly controversial, and it drew objections from both industry and Congress regarding FDA's approach to intended use.[74] Tellingly, however, the 2011 draft IVD guidance did not include the "totality" standard, which was seemingly created out of thin air for the final guidance in 2013.[75] In short, the Final Rule is attempting to codify a highly controversial standard that is inconsistent with the statute and case law and has never been subjected to public scrutiny.

In addition, the "totality" standard set out in the Final Rule is directly contrary to the case law constraining FDA's ability to rely on "circumstantial" evidence. In *NNFA v. FDA*, the Second Circuit indicated that a vitamin product could be found a drug under the statutory definition even without label claims of a product's therapeutic value, but such a finding would have to be based on "something more than demonstrated uselessness" as a non-therapeutic product "for most people."[76] A few years later, the Second Circuit indicated that FDA might establish a "drug" intended use by showing that the vitamins had been "used *almost exclusively* for therapeutic purposes."[77] After a remand, the Second Circuit then held in *NNFA v. Mathews* that FDA could not discharge its burden. The court found that, because the agency failed to show that therapeutic use "*far outweighed* [the products'] use as dietary supplements," and because none of the promotional materials cited by the agency were attributable to the manufacturers, the agency could not show that the vitamins were intended to be used as drugs.[78] Following the *NNFA* cases, the D.C. Circuit held in *ASH v. Harris* that "consumers must use the

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[73] According to that document, the intended use of a product "may be determined by looking at the totality of circumstances surrounding the distribution of the article." FDA, *Guidance for Industry and FDA Staff: Distribution of In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only*, 9 (2013).

[74] *See, e.g.*, AdvaMed, Comment to Docket No. FDA-2011-D-0305, 2 (Aug. 26, 2011); Mayo Clinic, Comment to Docket No. FDA-2011-D-0305, 1 (Aug. 29, 2011); *see also* Letter from Members of the Congressional Subcommittee on Health to Margaret A. Hamburg, Commissioner, FDA, 1 (Mar. 19, 2012) ("The Draft Guidance Document appears to represent a disregard of current law on 'intended use.").

[75] *See generally* FDA, *Draft Guidance for Industry and FDA Staff: Commercially Distributed In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only: Frequently Asked Questions* (2011).

[76] *NNFA v. FDA*, 504 F.2d at 789.

[77] *NNFA v. Weinberger*, 512 F.2d 688, 703 (2d Cir. 1975) (emphasis added).

[78] *NNFA v. Mathews*, 557 F.2d at 336 (emphasis added).

product *predominantly*—and in fact *nearly exclusively*—with the appropriate intent before the requisite statutory intent can be inferred."[79]

We are aware of exactly *one* case where this exacting test was effectively met. In 2001, a district court found that sellers of nitrous oxide balloons at a rock concert in Washington, D.C. intended for the gas to be used as a drug despite the government's inability to introduce any labeling or advertising materials into evidence.[80] In that case, "*[t]he government argue[d]* that the Court should . . . view *the totality of the circumstances*" to find an intended drug use for the nitrous oxide balloons.[81] But the court did not actually endorse the government's "totality" argument as its own view. Instead, the court followed *ASH v. Harris* and stated that evidence of "'consumer intent'" could be relevant if it is "'strong enough to justify an inference as to the vendor's intent.'"[82] The court then held that, under the "obviously unique" facts of that case, "the sellers did not need to label or advertise their product" because the "environment provided the necessary information between buyer and seller."[83]

These cases do not reflect a totality standard, but rather establish that FDA may rely on circumstantial evidence of consumer intent only when its probative value is sufficient to *negate* any explanation other than the intended use of the product as a drug or device. Under a totality standard, however, FDA would be free to determine where the balance of evidence lies and to ascribe whatever probative value it chooses to circumstantial evidence, or at least could argue that another fact finder could do so. Under such a scheme, facts of even marginal relevance can be considered as part of a larger mix of circumstances, even if the probative force of each fact is relatively weak. That would be a substantial change in the law.[84]

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[79] *ASH v. Harris*, 655 F.2d at 240 (emphasis added).

[80] *See United States v. Travia*, 180 F. Supp. 2d 115, 118-19 (D.D.C. 2001).

[81] *Id.* at 118 (emphasis added).

[82] *Id.* at 119 (quoting *ASH v. Harris*, 655 F.2d at 239).

[83] *Id.* The preamble to the Final Rule also cites *United States v. 789 Cases, More or Less, of Latex Surgeons' Gloves, an Article of Device*, 799 F. Supp. 1275, 1285 (D. Puerto Rico 1992), as a purported example of a court finding an intended use based on the circumstances surrounding the product's sale. Any commentary to that effect in *Surgeons' Gloves* is dicta. The manufacturer in that case had "represented that its gloves were to be used as surgeons gloves or as dental examination gloves." *Id.* at 1280. Because the manufacturer had "created a market for [its] product to be used as a device," the district court refused to entertain the manufacturer's *post hoc* assertions that "the product has a different—and non-regulated use." *Id.* at 1285.

[84] FDA claims that it previously "relied on circumstantial evidence of intended use" to target "street drug alternatives" and/or counterfeit drugs that had been deliberately mislabeled. 82 Fed. Reg. at 2208. The examples provided in the preamble to the Final Rule were not accompanied by citation to any judicial decision, and most of the examples appear to be referring to FDA warning letters or similar correspondence. *See, e.g.*, Warning Letter to Global Vision Product (Apr. 3, 2003); Warning Letter to Legal Gear and Affordable Supplements (Mar. 8, 2006); Warning Letter to Kanec USA, Inc. (Oct. 8, 2010). Warning letters and other agency correspondence are, however, merely statements by FDA employees and are not subject to judicial review. *See Holistic Candlers & Consumers*

Similarly, the preamble to the Final Rule indicates that the totality standard is meant to allow FDA to scrutinize internal company documents to find an intended use, even if those documents have not been published to the marketplace.[85] FDA relies primarily on an *in limine* ruling from the district court in *United States v. Vascular Solutions, Inc.*, a case in which the government stated that it would rely "on promotional speech . . . alone," but where the court nevertheless addressed the admissibility of a *hypothetical* bumper sticker locked in a briefcase and never made public.[86] While touting a pre-trial ruling concerning hypothetical facts, FDA failed to discuss an Eighth Circuit case that dealt with that scenario in real terms—and reached a contrary conclusion. In *United States v. Articles of Drug for Veterinary Use*, the Eighth Circuit upheld a jury verdict for the defendant and held that the government could not rely on written materials stored in a warehouse as evidence of intended use because the government failed to establish that they "were promotional in nature" or "were ever distributed in relation to the six products seized."[87] The omission of cases that do not support FDA's preferred interpretation shows that the Final Rule is trying to change the law and settle difficult legal issues in the agency's favor without even acknowledging contrary precedent.

Further, FDA misunderstands the case law suggesting that the government can consider "any relevant source" in assessing the manufacturer's intended use.[88] Those cases merely state that any relevant source *of claims* is potentially relevant to the intended use inquiry. The phrase has its roots in *United States v. 3 Cartons . . . "No. 26 Formula GM,"* where the manufacturer had attempted to avoid regulation as a drug by omitting and even disclaiming therapeutic uses in the *label* for its product.[89] The court rejected that argument, finding authority to consider "any source which discloses the intended use."[90] In particular, the court relied on the "literature" disseminated by the manufacturer, which had "consistently represented these products as efficacious in the treatment, mitigation, and prevention of many ailments including some of the most serious that afflict mankind."[91]

Ass'n v. FDA, 664 F.3d 940, 941-42 (D.C. Cir. 2012). Those letters are not the law, and they provide no support for FDA's proposal to expand intended use by adding a new totality standard to 21 C.F.R. §§ 201.128 and 801.4. *See, e.g., Sottera, Inc. v. FDA*, 627 F.3d 891, 897 (D.C. Cir. 2010) ("FDA's claimed authority" in a warning letter was irrelevant because it was "never challenged or adjudicated in court.").

[85] *See* 82 Fed. Reg. at 2207-08.

[86] *See United States v. Vascular Solutions, Inc.*, 181 F. Supp. 3d 342, 346 (W.D. Tex. 2016).

[87] *United States v. Articles of Drug for Veterinary Use*, 50 F.3d 497, 501 (8th Cir. 1995).

[88] *See* 82 Fed. Reg. at 2206 ("FDA's longstanding position is that, in determining a product's intended use, the Agency may look to any relevant source of evidence. This position has solid support in the case law.").

[89] *See United States v. 3 Cartons . . . "No. 26 Formula GM,"* 132 F. Supp. 569, 573 (S.D. Cal. 1952).

[90] *Id.* at 574.

[91] *Id.* at 573.

Virtually all of the cases cited by FDA follow the same pattern. Thus, in *V.E. Irons, Inc. v. United States*, the First Circuit stated that it could "look at all relevant sources" in response to an argument that the intended use analysis should be "confined to the labels on the drug or the 'labeling.'"[92] The court found that the relevant sources were "all of appellants' literature as well as the oral representations made by [its president] at his lectures or by authorized sales distributors."[93] At no point did the court consider evidence beyond the manufacturer's affirmative representations regarding its products.

The Second Circuit's decision in *Sudden Change* provides still more confirmation that FDA's totality approach has no basis in the law. In that case, the court coined the phrase that "the intended use of a product may be determined from its label, accompanying labeling, promotional material, advertising and any other relevant source."[94] In explaining this test, the court made clear that it applies only to certain types of promotional claims:

> Regardless of the actual physical effect of a product, it will be deemed a drug for purposes of the Act *where the labeling and promotional claims show intended uses* that bring it within the drug definition. . . . Thus, Congress has made a judgment that a product is subject to regulation as a drug *if certain promotional claims are made for it.*[95]

Indeed, every one of the nine cases cited in the *Sudden Change* opinion considered only promotional claims.[96]

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[92] *V.E. Irons, Inc. v. United States*, 244 F.2d 34, 44 (1st Cir. 1957).

[93] *Id.*

[94] *Sudden Change*, 409 F.2d at 739.

[95] *Id.* (emphases added). That "any relevant source" is limited to sources *of promotional claims* like labeling and advertising also is confirmed by the canon of *ejusdem generis*—when general words like "any other relevant source" follow specific words (here, "labeling, promotional material, and advertising"), the general words are said to embrace "only objects similar in nature to those objects enumerated by the preceding specific words." *Yates v. United States*, 135 S. Ct. 1074, 1086 (S. Ct. 2015) (citations omitted).

[96] *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"); *Bradley*, 264 F. at 82 (water held to be a drug under the 1906 Act when marketed subject to therapeutic claims); *United States v. 354 Bulk*

Later cases, including those cited by FDA, also relied on promotional claims to find an intended use rather than an ad hoc, "totality" approach. For example, the district court decisions in both *Hanson v. United States* and *United States v. Undetermined Quantities of an Article of Drug Labeled as "Exachol,"* incorporated the same language and citations from *Sudden Change*, and also relied on explicit promotional claims to find an intended use.[97] Similarly, the district court decisions in *United States v. Lane Labs-USA, Inc.* and *United States v. Kasz Enterprises, Inc.* also relied on explicit claims to find intended drug uses.[98]

Even as to the specific question of manufacturer knowledge, the Final Rule represents a change in FDA's own position. The agency itself has previously argued that awareness of an actual use cannot be used to show an intended use, even if there is corroborating evidence.[99] In several instances, FDA has argued that the product's labeling determines its intended uses.[100] Codifying a totality of the evidence standard in 21 C.F.R. §§ 201.128 and 801.4 would change that position without addressing FDA's prior contrary interpretations.

FDA's citation to *United States v. Storage Spaces Designated Nos. 8 and 49* is particularly inapposite. FDA claims that the Ninth Circuit relied on "'the overall circumstances'" to find an intended use for drugs that were "innocuously labeled" but actually contained imitation cocaine.[101] However, the phrase "overall circumstances" appears only in a

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Cartons Trim Reducing-Aid Cigarettes, 178 F. Supp. 847, 851 (D.N.J. 1959) ("Claimant readily concedes that its product is intended to affect the structure and functions of the human body by reducing the appetite for the ingestion of food and thereby achieving a reduction in the body's weight."); *Fairfax Cigarettes*, 113 F. Supp. at 339 ("The clear import of the leaflet is at least that the smoking of the cigarettes will make it less likely that the smoker will contract colds or other virus infections."); *26 Formula GM*, 132 F. Supp. at 573-74 (considering "claimant's literature").

[97] *Hanson v. United States*, 417 F. Supp. 30, 35 (D. Minn. 1976) ("The promotional materials . . . make similar claims" that "the ingestion of laetrile results in the 'prevention, control, arrest and minimization of cancerous tissue growths.'"), *aff'd*, 540 F.2d 947 (8th Cir. 1976) (*per curiam*); *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.").

[98] *United States v. Lane Labs-USA, Inc.*, 324 F. Supp. 2d 547, 568 (D.N.J. 2004) ("many of the materials at issue in this action blatantly claimed that the given product was an effective treatment for cancer or HIV/AIDS"); *United States v. Kasz Enters., Inc.*, 855 F.Supp. 534, 540 (D.R.I. 1994) ("The promotional materials accompanying Solutions 109 are replete with claims (testimonials) that hair growth has occurred and hair loss prevented with use of these products.").

[99] *Sigma-Tau*, 288 F.3d at 145.

[100] *See id.* at 146 ("The FDA determined the intended use for [the] generic drugs by relying primarily upon the proposed labeling provided by the companies."); *Spectrum Pharms., Inc. v. Burwell*, 824 F.3d 1062, 1067 (D.C. Cir. 2016) ("FDA responds that it need look no further than the use indicated in [the abbreviated new drug application] . . . We agree with FDA . . . ."); *see also* Ribavirin Petition Response, supra note 21, at 22 ("Here, the proposed labeling would be the most relevant and compelling, if not exclusive, manifestation of the objective intent of the ANDA applicant legally responsible for that proposed generic ribavirin capsule drug product.").

[101] 82 Fed. Reg. at 2208.

footnote rebutting the defendants' arguments that their products' labels should be controlling as to the products' intended uses.[102] In the main text, the court determined that the products were intended for use as drugs based on "leaflets," a "flyer," and "catalogs and advertisements," all of which claimed "that the products could produce stimulation, as cocaine does."[103]

The Agency's reliance on *United States v. An Article of Device Toftness Radiation Detector* is also misplaced. The Seventh Circuit had no occasion to evaluate the sufficiency of the evidence of intended use presented at trial, much less the propriety of a "totality of evidence" standard, because the defendants did not challenge the evidence. In fact, they introduced much of the evidence themselves, and argued that it showed that their device "was not intended to be used as the *sole* means of diagnosing patients" and that their device was "intended only for research."[104] The court determined that both arguments failed as a matter of law, explaining that an "instrument need not be the only agent in an allegedly curative process to be a device within the definition," and that "the Act and its regulations do not except instruments involved in research from the definition of 'device.'"[105]

Finally, FDA cites the D.C. Circuit's opinion in *ASH v. Harris*, but that case holds that "the crux of FDA jurisdiction over drugs lay in manufacturers' representations as revelatory of their intent" and that this "understanding has now been accepted as a matter of statutory interpretation."[106] Far from embracing the totality standard that FDA posited, the D.C. Circuit rejected the argument that the intended use of cigarettes should be inferred from the circumstances surrounding their manufacture and distribution.[107]

b. The totality standard would introduce significant constitutional concerns.

As explained in the prior section, the cases interpreting "intended use" under the FDCA do not allow the agency to consider any and all categories of evidence, without limits, to show an intended use. Instead, cases hold that intended uses "must be determined from objective evidence in promoting, distributing, *and* selling the [drug or] device."[108] In particular, a manufacturer *must* make an explicit promotional claim before FDA may find a new intended use.

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[102] *United States v. Storage Spaces Designated Nos. 8 and 49*, 777 F.2d 1363, 1366 n.5 (9th Cir. 1985).

[103] *Id.* at 1366.

[104] *United States v. An Article of Device Toftness Radiation Detector*, 731 F.2d 1253, 1257 (7th Cir. 1984) (emphasis added).

[105] *Id.* at 1258.

[106] *ASH v. Harris*, 655 F.2d at 238-39.

[107] *Id.* at 239-40.

[108] *United States v. One Unlabeled Unit, More or Less of an Article of Device and Promotional Brochures*, 885 F. Supp. 1025, 1028 (N.D. Ohio 1995) (emphasis added).

FDA's totality standard not only departs from existing law, but also raises serious constitutional concerns.

To be sure, the traditional claims-based interpretation of intended use, which predated the development of contemporary commercial speech case law, raises challenging First Amendment questions.[109] Moreover, a vague standard allowing the prosecution of manufacturers for misbranding violations based merely on inferences of promotional claims drawn from the "totality of circumstances" violates the Due Process clause of the Fifth Amendment by failing to provide regulated parties "fair notice of conduct that is forbidden or required."[110] These concerns are heightened when the lack of clarity chills protected speech.[111]

FDA's new "totality of the evidence" test all but guarantees significant constitutional harms will result. For instance, the Final Rule exacerbates the already intolerable uncertainty that FDA's regulations and enforcement actions have created with respect to the boundaries of criminal liability. As the MIWG explained in its 2013 citizen petition, the Due Process Clause of the Fifth Amendment requires that the government regulate with "precision" in this arena and provide fair notice to regulated industry as to the conduct that can (and cannot) lead to potential liability.[112] As the MIWG also explained, the lack of *a priori* rules clearly defining and limiting the government's ability to allege an intended use under 21 C.F.R. §§ 201.128 and 801.4 violates those due process principles because the open-ended intended use regulations leave manufacturers unable to evaluate, in advance, the lawfulness of proposed business practices.[113] Experience has shown that prosecutors (and the private *qui tam* bar) have relied on 21 C.F.R. §§ 201.128 and 801.4 to allege *after the fact* that business practices have misbranded a product because they provide circumstantial evidence of an intended use, even if that use was in no way promoted by the defendant. Codifying a "totality" standard in the intended use regulations will

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[109] In *United States v. Caronia*, the court held that truthful and non-misleading promotional claims are protected by the First Amendment, and invoked the canon of constitutional avoidance to adopt a construction of the FDCA that obviated a collision between FDA's implementation of the statute and important constitutional restrictions on the agency's power to regulate manufacturer communications. *See* 703 F.3d 149, 160, 162 (2d Cir. 2012); *see also Amarin Pharm., Inc. v. FDA*, 119 F. Supp. 3d 196, 225 & n.56 (S.D.N.Y. 2015). FDA currently is engaged in a "comprehensive review" of its regulatory scheme, which has involved a public hearing and, more recently, the agency's publication of a lengthy memorandum reflecting its perspective on the application of First Amendment principles to its regulatory authorities under the FDCA. *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).

[110] *FCC v. Fox Television Stations, Inc.*, 132 S. Ct. 2307, 2317 (2012).

[111] *Id.* at 2318 (fair notice principles operate with greater force "when applied to . . . regulations that touch upon 'sensitive areas of basic First Amendment freedoms'") (quoting *Baggett v. Bullitt*, 377 U.S. 360, 372) (1964)).

[112] Citizen Petition, Docket No. FDA-2013-P-1079, at 8 (Sept. 3, 2013).

[113] *Id.* at 15-19.

only make these problems worse. Under a totality standard, no one will be able to know, in advance, what evidence (or even types of evidence) a prosecutor might consider sufficient to deem an actual use to be an intended use, raising significant Fifth Amendment concerns.

Similarly, and as discussed below, the new "totality" standard would not only risk the restriction of truthful and non-misleading promotional speech, but also chill non-promotional speech that FDA has consistently recognized as beneficial to the public health.

c. The totality standard would negatively impact the public health by chilling valuable scientific speech.

Under a "totality of the evidence" standard, everything may be considered to establish a product's intended use. This standard would allow FDA to rely even on non-promotional scientific exchange as evidence of intended use. Such evidence could include speech with significant public health benefits, including a firm's distribution of reprints, clinical practice guidelines, or reference texts regarding unapproved uses of approved/cleared medical products; its responses to unsolicited requests for information about such uses; its presentation of truthful and non-misleading scientific information about unapproved uses at medical or scientific conferences; and its discussions of such uses with third-party payers. Although FDA has issued *non-binding* guidance documents or draft guidance documents concerning some of these activities, any such statements appear to be trumped by the *binding* totality standard codified at 21 C.F.R. §§ 201.128 and 801.4.

The chilling effect of such a standard is difficult to overstate. For example, if a company engages in scientific exchange about off-label use, forecasts on- and off-label sales, and scales production to meet the combined demand, a prosecutor could decide that this evidence reflects an off-label intended use. Combined with the substantial penalties and resulting pressure companies face to settle criminal misbranding cases, the new intended use rule exposes manufacturers to a significant risk of liability for conduct that is entirely lawful and beneficial to the public health. The result of the Final Rule is therefore that speech regarding valuable scientific and medical information will be chilled, negatively impacting the public health.

IV. Conclusion

For the foregoing reasons, reconsideration should be granted, the Final Rule published on January 9, 2017 should be indefinitely stayed, and FDA staff should promulgate final intended use definitions consistent with the definitions set out in the September 2015 notice of proposed rulemaking.

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