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ROPES & GRAY

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Via Electronic Submission

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

Re: Amendments to Regulations Regarding "Intended Uses"; Proposed Partial Delay of Effective Date (Docket Nos. FDA-2015-N-2002, FDA-2017-D-4792, and -6580)

These comments are submitted on behalf of the Medical Information Working Group (MIWG), in response to (1) the Federal Register notice published by the Food and Drug Administration (FDA) on January 16, 2018 (83 Fed. Reg. 2092) ("the January 16 notice"), and (2) FDA's January 12, 2018, statement accompanying the notice ("the January 12 statement").[1] 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.[2]

We commend FDA for taking steps to delay the effective date of the amendments to the agency's existing intended use regulations at 21 C.F.R. §§ 201.128 and 801.4. We further commend FDA for committing to "further consideration of the substantive issues raised in the comments received" on the final rule published in the Federal Register on January 9, 2017 ("the Final Rule").[3] In our comments, we focus on one specific issue: the need for FDA to confirm its *current* interpretation of intended use, while the agency continues its process of evaluating the comments received on the Final Rule.

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[1] Statement from FDA Commissioner Scott Gottlieb, M.D., on FDA Decision To Seek Additional Time To Reassess Rule That Would Have Changed Longstanding Practices For How the Agency Determined The "Intended Use" of Medical Products (Jan. 12, 2018), http://bit.ly/2Fx2EYe.

[2] 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 Pharmaceuticals Corporation; Pfizer Inc.; Sanofi US; and Samumed, LLC. The MIWG's prior submissions to FDA are available at www.miwg.org.

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

As we discuss further below, the MIWG believes that FDA should clarify that its current interpretation of intended use is the interpretation that is included in the preamble accompanying the September 25, 2015 proposed rule. According to that preamble and its referenced authorities, FDA will not assert that a new intended use has been created by the knowledge of the manufacturer, without more, or that a new intended use has been created by such knowledge together with non-promotional speech (*e.g.,* reprints disseminated as described in applicable FDA guidance). In addition, the MIWG believes that FDA should assure that guidance documents and other policy pronouncements which describe intended use do so only in a manner that is consistent with current FDA policy, as reflected in the proposed rule preamble and cited authorities.

I. FDA Should Affirm Its Current Position On Intended Use

"Intended use" under the FDCA has a specific meaning. From the outset, the "intended use" prong of the drug definition related to the manufacturer's clear promotional claims for its products. When the FDCA was enacted in 1938, its sponsors made clear that intended use would turn on representations by the manufacturer.[4] 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.[5]

Courts and FDA have treated this legislative history as authoritative.[6]

Because they do not, by their terms, strictly adhere to the claims-based interpretation, FDA's intended use regulations at 21 C.F.R. §§ 201.128 and 801.4 have long been controversial. For example, in 1998, FDA published a rule purporting to require manufacturers of approved drugs "to provide adequate labeling" regarding pediatric use, even if such use was neither claimed nor recommended.[7] Citing 21 C.F.R. § 201.128, FDA contended that an approved drug's intended uses include "the actual

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[4] *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").

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

[6] *See, e.g., NNFA v. FDA*, 504 F.2d 761, 789 & n.35 (2d. Cir. 1974) (concluding that FDA had erred in attempting to regulate vitamins as drugs absent therapeutic claims); *United States v. Article of 216 Cartoned Bottles, "Sudden Change,"* 409 F.2d 734, 736, 739 & n.3 (2d Cir. 1969) (holding cosmetic lotion a drug because "labeling and promotional claims show intended uses that bring it within the drug definition); *United States v. 46 Cartons . . . Fairfax Cigarettes*, 113 F. Supp. 336, 337 (D.N.J. 1953) (holding that cigarettes marketed with therapeutic claims were properly categorized as drugs). *See also* 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).

[7] 63 Fed. Reg. 66,632 (Dec. 2, 1998).

uses of the drug of which the manufacturer has, or should have, notice, even if those uses are not promoted by the manufacturer."[8] 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."[9] The court found the agency's reliance on § 201.128 unavailing, as "'no order or regulation issued by an administrative agency can confer on it any greater authority than it has under the statute.'"[10]

More recently, FDA's intended use definition has been challenged as an unconstitutional restraint on protected speech regarding unapproved uses of approved medical products.[11] In that context, the government has articulated limiting interpretations of 21 C.F.R. § 201.128—including one that denies mere manufacturer knowledge can comprise a new intended use.[12]

Our members filed two citizen petitions that urged FDA to revise the regulations to remove the knowledge prong, and we submitted comments in support of the September 2015 proposed rule. There, FDA explains that it

> does not 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 (see Ref. 5). Accordingly, FDA is taking this opportunity to amend §§ 201.128 and 801.4 to better reflect FDA's interpretation and application of these regulations. These changes would not reflect a change in FDA's approach regarding evidence of intended use for drugs and devices.

In this passage, FDA emphasizes that, under the interpretation of the law that was then in effect and that had been in effect for some unspecified period before the proposed rule, a manufacturer's knowledge

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[8] *Id.* at 66,658.

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

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

[11] *See* Compl., *Par Pharm., Inc. v. United States*, No. 11-1820, Dkt. 1, ¶ 85 (D.D.C. filed Oct. 14, 2011); Compl., *Allergan, Inc. v. United States*, No. 09-1879 Dkt. 1-2, ¶¶ 94, 132-33, 135 (D.D.C. filed Oct. 1, 2009).

[12] *See, e.g.*, Oral Arg. Tr. at 10, *United States v. Caronia*, No. 09-5006 (2d Cir. Dec. 2, 2010) (in response to the court asking 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," government counsel replied: "I believe not, Your Honor, I don't think that would be a crime"); Defs.' Mem. in Supp. of Mot. to Dismiss or for Summ. J. at 27- 28, *Par Pharm., Inc. v. United States*, No. 11-cv-1820, Dkt. 14-1 (D.D.C.) (rejecting the view that "knowledge of unapproved uses is sufficient by itself to establish intent"); Defs.' Mem. of P&A in Supp. of Mot. to Dismiss or for Summ. J. at 22, *Allergan v. United States*, No. 09-cv-01879, Dkt. 26-1 (D.D.C. Jan. 7, 2010) ("Allergan is wrong when it suggests that it 'commits a crime'. . . if it 'merely has knowledge or notice of an off-label use.'").

alone would not constitute a new intended use. But the preamble includes an important additional insight regarding the scope of the agency's interpretation.

Relying on a government brief in the *Allergan* litigation,[13] the preamble states that, "[i]n practice, FDA usually does not treat an unapproved use as an intended use solely because the manufacturer knows that the unapproved use is taking place." The government brief, in turn, cites an FDA declaration, also filed in the *Allergan* litigation, stating that the agency "would not ordinarily regard a manufacturer as intending an off-label use for an approved product based solely on the manufacturer's knowledge that an approved product was being prescribed by doctors for such use, and even if the sponsor provided scientific articles about such use."[14] The declaration continues by citing—as one example—manufacturer dissemination of journal articles describing off-label uses as an additional potential evidence source that FDA will not regard as creating an intended use when combined with the manufacturer's knowledge.[15] It then explains that a manufacturer can go farther, by "providing appropriate warnings about the adverse consequences of an off-label use," and that not even that speech would be regarded by the agency as "evidence of intended use."

From these sources, it is clear that FDA cannot find an intended use for a drug or medical device based solely on the manufacturer's knowledge of a product's use. It appears, further, that FDA does not believe it can find an intended use based on the manufacturer's knowledge even when combined with the manufacturer's dissemination of non-promotional materials such as reprints of journal articles describing an off-label use, or with the manufacturer's provision of risk information about an off-label use. As long as the manufacturer avoids any explicit or implicit promotion of "efficacy of the unapproved use," FDA will not point to any of these communications as within the scope of §§ 201.128 and 801.4. According to the preamble, therefore, a manufacturer can engage in certain external communications *and* have knowledge of an off-label use without risking that FDA will cite them as evidence of intended use.

Unfortunately, however, as FDA has recognized, the agency's ongoing rulemaking proceeding—and in particular, the new language in the Final Rule purporting to allow FDA to determine intended use based on the "totality of the evidence"—creates "the potential for confusion."[16] FDA has stated that the "totality" language represents the position that the agency had always taken on intended use.[17] Under the "totality" standard, however, activities that are effectively prohibited are clearly permitted under the approach to intended use that is reflected in the preamble accompanying the proposed rule and the

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[13] FDA cites Reference 5, Defendant's Memorandum of Points and Authorities In Support of Motion to Dismiss or Summary Judgment, in *Allergan Inc., v. United States of America*, 1:09-cv-01879-JDB (D.D.C. Jan. 11, 2010).

[14] Decl. of Dr. Robert Temple ¶ 9, *Allergan v. United States*, No. 09-1879 (D.D.C. Dec. 11, 2009). The government cites paragraph 10 of the Declaration, but "knowledge" is discussed in paragraph 9.

[15] *Id.*

[16] 83 Fed. Reg. at 2095.

[17] 82 Fed. Reg. at 2205-06; 82 Fed. Reg. 14,319, 14,320 (Mar. 20, 2017) ("The revised sentence was . . . intended to embody FDA's longstanding position . . . .").

authorities cited by FDA in the preamble. It is hard to reconcile the "totality of the evidence" language in the Final Rule with FDA's own accompanying explanatory statements. It is also hard to square the "totality" language with FDA's well-established position with respect to the importance of manufacturer communications about new uses of approved products to patient care, or with the relevant judicial decisions and other applicable law which defines intended use with reference to promotional claims by the manufacturers.[18]

Moreover, although the agency's intended use rulemaking remains pending, two guidance documents have been published—one by CDRH and another by CDER—that treat contested issues of interpretation in this area as settled agency policy. A draft guidance document on microneedling devices asserts that intended use can be determined according to not only the manufacturer's claims but also product design, technological characteristics/features, and "any other relevant source."[19] Similarly, draft guidance on homeopathic drug products states that CDER can find intended use based on whether "a product purports to be or is represented as a product recognized in an official compendium,"[20] irrespective of manufacturer claims and despite contrary case law.[21] These guidance documents provide additional evidence of confusion in the current regulatory scheme over FDA's interpretation of intended use, and further point up the need for FDA to provide an interim clarification, not only for regulated entities but also for agency staff.

To address "the potential for confusion" recognized by FDA, we request that the agency confirm, during the pendency of the rulemaking process, that (1) mere knowledge does not constitute an intended use and (2) knowledge in combination with safe harbored non-promotional communications (*e.g.*, reprints, information regarding the risks associated with an off-label use as described in the declaration filed by FDA in the *Allergan* case) would not constitute a new intended use. Doing so would provide much-needed clarity to regulated industry and FDA personnel and would help ensure that manufacturers do not refrain from sharing truthful, non-misleading information that is beneficial to the public health.

II. Conclusion

The MIWG fully supports FDA's decision to take additional time to evaluate the issues that have been raised in the intended use rulemaking since the agency published its proposed rule in September 2015. We submitted comments in support of the proposed rule, but the Final Rule's precipitous adoption of a broad and unsupported "totality" standard raised highly significant legal issues. As a

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[18] *See, e.g.*, MIWG, Comments on "Intended Use" Final Rule, Docket No. FDA-2015-N-2002, 3-11 (July 18, 2017); MIWG, PhRMA, & BIO, Petition to Stay and for Reconsideration, Docket No. FDA-2015-N-2002, 7-10 (Feb. 8, 2017).

[19] FDA, Regulatory Considerations for Microneedling: Draft Guidance for Industry and FDA Staff, at 7-8 (Sept. 15, 2017). *See also* MIWG, Comments on Microneedling Draft Guidance, Docket No. FDA-2017-D-4792 (Nov. 14, 2017), http://bit.ly/2FWvzVy.

[20] FDA, Drug Products Labeled as Homeopathic: Draft Guidance for FDA Staff and Industry, at 5 (Dec. 2017).

[21] *See, e.g., Nat'l Nutritional Foods Ass'n v. FDA*, 504 F.2d 761, 788-89 (2d Cir. 1974).

result, the MIWG asked FDA to reconsider that standard, and we commend the agency for its decision to reevaluate the Final Rule.

We also believe, however, that it is critically important for FDA to communicate clearly its position on intended use while the rulemaking proceeding continues. As we understand it, FDA's current position, consistent with the preamble to the September 2015 proposed rule, is that knowledge alone does not create a new intended use, and that knowledge in combination with non-promotional communications about a new use also does not create a new intended use.

We also urge FDA to make additional changes to the intended use regulations to make them more consistent with applicable law. We refer the agency to our comments submitted on the September 2015 proposed rule for additional information regarding the changes that we believe deserve careful consideration, as well as to our submissions regarding the Final Rule for additional detail on the MIWG's position with respect to intended use. Until revised regulations are finalized, guidance and other policy pronouncements announced by FDA must describe intended use consistently with the agency's current stance on this pivotal regulatory concept, as articulated in the proposed rule and cited authorities.

Respectfully submitted,

Coleen Klasmeier
Paul Kalb
SIDLEY AUSTIN LLP
1501 K Street, NW
Washington, DC 20005
(202) 736-8000

Kellie B. Combs
Doug Hallward-Driemeier
ROPES & GRAY, LLP
2099 Pennsylvania Avenue, NW
Washington, DC 20006-6807
(202) 508-4730

Joan McPhee
ROPES & GRAY, LLP
1211 Avenue of the Americas
New York, NW 10036
(212) 596-9443

Counsel to the Medical Information Working Group

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