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

Re: Clarification of When Products Made or Derived From Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses"; Further Delayed Effective Date; Request for Comments, Docket No. FDA-2015-N-2002, 82 Fed. Reg. 14319 (Mar. 20, 2017)

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America ("PhRMA") appreciates the opportunity to comment in response to FDA's March 20, 2017 notification further delaying the effective date of, and seeking comments on, the Agency's January 9, 2017 final rule amending existing regulations regarding "intended uses," including 21 C.F.R. § 201.128 ("Request for Comments").[1] PhRMA members are devoted to discovering and developing medicines that enable patients to live longer, healthier, and more productive lives. Since 2000, PhRMA's member companies have invested more than half a trillion dollars in the search for new treatments and cures, including an estimated $58.8 billion in 2015 alone.

PhRMA commends FDA for reopening the final rule amending the intended use regulations ("Final Rule")[2] for further comments in recognition of the important issues raised in the Petition to Stay and for Reconsideration of the Final Rule submitted by the Medical Information Working Group ("MIWG"), PhRMA, and the Biotechnology Innovation Organization ("BIO") ("Petition").[3] As FDA acknowledged in its Request for Comments, the Petition raises "important substantive issues" about the Final Rule's amendments to the intended use regulations.[4]

We also recognize that FDA has recently requested comments on several other documents regarding manufacturer communications with healthcare professionals, payors, and other population health decision-makers, including: (1) FDA's notification of public hearing about manufacturer communications regarding unapproved uses of approved or cleared medical

[1] 82 Fed. Reg. 14319 (Mar. 20, 2017).

[2] 82 Fed. Reg. 2193 (Jan. 9, 2017).

[3] MIWG, PhRMA, and BIO, Petition to Stay and for Reconsideration (Feb. 8, 2017).

[4] 82 Fed. Reg. at 14320 (discussing the Petition).

products and related Memorandum entitled "Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products" ("First Amendment Memorandum");[5] (2) FDA's draft guidance regarding manufacturer communications with payors, formulary committees, and similar entities;[6] and (3) FDA's draft guidance regarding manufacturer communications with healthcare professionals that are consistent with the FDA-approved labeling.[7] On April 19, 2017, PhRMA submitted three separate comment letters in response to those documents. Some of the issues PhRMA addressed in those comment letters overlap with issues raised by the Final Rule.

These comments specifically relate to PhRMA's grave concerns about the Final Rule. The Final Rule asserts that a product's "intended use" may be shown if "the totality of the evidence establishes that a manufacturer objectively intends that a drug introduced into interstate commerce by him is to be used for [an unapproved use]."[8] It further contends that, although FDA would not bring an enforcement action based "solely" on a manufacturer's knowledge that a FDA-approved product was being used for an unapproved use, "[i]f there is other evidence of intended use, FDA may consider manufacturer knowledge as well as other evidence."[9] And the Final Rule maintains that FDA may consider "*any* claim or statement by or on behalf of a manufacturer that explicitly or implicitly proposed a product for a particular use."[10] In this regard, FDA "does not agree with the assertion that the current case law allows FDA to consider speech as evidence of intended use only when it is false or misleading."[11]

As an initial matter, PhRMA believes that FDA may establish that a manufacturer has a particular "intended use" for an article *only* when the manufacturer has made a promotional claim about that use to a third party. The Final Rule adopts an expansive "totality of the evidence" standard under which a particular "intended use" may be established even absent any external manufacturer claim about that use. Such an approach is simply not supported by the case law. We are aware of no case in which a court has found that an "intended use" of a product was established absent an external claim by the manufacturer about the use.

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[5] 81 Fed. Reg. 60299 (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 (Jan. 2017).

[6] FDA, Draft Guidance, Medical Product Communications That Are Consistent With the FDA-Required Labeling—Questions and Answers (Jan. 2017).

[7] FDA, Draft Guidance, Drug and Device Manufacturer Communication with Payors, Formulary Committees, and Similar Entities—Questions and Answers (Jan. 2017).

[8] 82 Fed. Reg. 2193, 2206.

[9] *Id.* at 2193, 2206.

[10] *Id.* at 2195 (emphasis added).

[11] *Id.* at 2193, 2209.

Further, if allowed to stand, the Final Rule would, in some circumstances, inappropriately restrict important speech about unapproved uses of FDA-approved medical products that could be beneficial to both healthcare professionals and the patients they serve. For example, as we explained in our comments responding to FDA's notification of public hearing and First Amendment Memorandum, in many cases prescribing FDA-approved medicines for unapproved uses is medically accepted and often is the standard of care.[12] The Final Rule suggests that FDA will treat manufacturers' communications about unapproved uses as rendering FDA-approved products misbranded in violation of the Food, Drug, and Cosmetic Act ("FDCA"), *even if those communications are truthful and non-misleading*. But the First Amendment permits FDA to restrict speech only as a last resort and places the burden squarely on FDA to justify any restrictions on speech by establishing that they directly advance a substantial government interest in a manner that "is not more restrictive than is necessary to serve that interest."[13] Recent case law, moreover, establishes that civil or criminal enforcement actions based on manufacturers' truthful and non-misleading communications about unapproved uses generally violate the First and Fifth Amendments. The Final Rule's overly broad restrictions on manufacturers' truthful and non-misleading communications with healthcare professionals about unapproved uses of approved products fail under these precedents, as there are clearly less-restrictive means to address FDA's regulatory concerns regarding such communications.

In this regard, in July 2016, PhRMA and BIO jointly published their "Principles on Responsible Sharing of Truthful and Non-Misleading Information About Medicines with Health Care Professionals and Payers" ("PhRMA-BIO Principles" or "Principles").[14] The PhRMA-BIO Principles set forth important concepts that PhRMA strongly endorses regarding manufacturer communications with healthcare professionals about unapproved uses. The Principles strike the constitutionally required balance between FDA's role in evaluating the safety and efficacy of new medicines and new uses of previously approved medicines, and the needs of patients for their healthcare providers and insurers to be fully educated about available treatment options. As explained in our comments submitted April 19, 2017, PhRMA urges FDA to adopt a Principles-based approach to regulation of manufacturer communications with healthcare professionals about unapproved uses.[15] This approach would adequately preserve FDA's legitimate interests without infringing upon the First Amendment rights of pharmaceutical manufacturers.

Manufacturer communications that adhere to the Principles are truthful and non-misleading and therefore fully protected under the First Amendment. In most circumstances, an enforcement action based on the notion that such communications render an approved product misbranded thus would violate the manufacturer's free speech rights. As explained below, we urge FDA to provide sufficient clarity, as required by the Due Process Clause of the Fifth Amendment, regarding the types of evidence that may be used to demonstrate intended use. We

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[12] *See* PhRMA, Comment to Docket No. FDA-2016-N-1149, 13-17 (Apr. 19, 2017).

[13] *Cent. Hudson Gas & Elec. Corp. v. Public Serv. Comm'n of N.Y.*, 447 U.S. 557, 557 (1980).

[14] *See* Appendix A.

[15] *See* PhRMA, Comment to Docket No. FDA-2016-N-1149 (Apr. 19, 2017).

therefore urge FDA to withdraw the Final Rule and to amend § 201.128 in a manner that complies with both statutory and constitutional restrictions on establishing "intended use."

BACKGROUND

On September 25, 2015, FDA issued a notice of proposed rulemaking ("Proposed Rule") seeking to resolve "ambiguity surround[ing] the circumstances under which a product that is made or derived from tobacco would be regulated as a drug, device, or combination product, and the circumstances under which it would be regulated as a tobacco product."[16] In addition to this tobacco-related issue, FDA sought to "provide clarity for drug and device manufacturers generally regarding FDA's interpretation and application of its existing intended use regulations," including 21 C.F.R. § 201.128.[17] Specifically, FDA explained 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."[18] FDA thus proposed to strike the last sentence of § 201.128, which provides that firms must provide "adequate labeling" for any unapproved use of a medicine about which a firm "knows, or has knowledge of facts that would give him notice."[19]

Other statements in the Proposed Rule, however, suggested that FDA intended to treat a pharmaceutical manufacturer's truthful and non-misleading communications with healthcare professionals about an unapproved use of an FDA-approved drug as establishing such use as the manufacturer's "intended use." For instance, FDA asserted that in determining a manufacturer's intended use, the Agency may consider "*any* claim or statement by or on behalf of a manufacturer that explicitly or implicitly proposed a product for a particular use."[20]

In its comments on the Proposed Rule submitted November 24, 2015, PhRMA commended FDA "for its clear statement that a manufacturer's mere 'knowledge' that its drug is being prescribed for an unapproved use will not establish such a use as the manufacturer's 'intended use.'" We supported FDA's proposal to eliminate the last sentence of § 201.128.[21] But we expressed concern about the Proposed Rule's statements suggesting that a drug's "intended use" may be established based on a manufacturer's truthful and non-misleading communications with healthcare professionals about an unapproved use.[22] Under this view, we explained, such truthful and non-misleading communications could render an FDA-approved

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[16] 80 Fed. Reg. 57756, 57756 (Sept. 25, 2015).

[17] 80 Fed. Reg. at 57758.

[18] *Id.* at 57761.

[19] 21 C.F.R. § 201.128.

[20] 80 Fed. Reg. at 57757 (emphasis added).

[21] *See* PhRMA, Comment to Docket No. FDA-2015-N-2002, 1 (Nov. 24, 2015).

[22] *See id.* at 2.

drug misbranded in violation of the FDCA. We urged FDA to "acknowledge both the public health value and the First Amendment protections afforded such communications [about unapproved uses], and that the FDCA does not prohibit them."[23] We further requested certain concrete changes to § 201.128 and other FDA regulations and guidance documents to provide greater clarity to industry and to align the Agency's approach to truthful and non-misleading communications with modern First Amendment jurisprudence.

FDA published the Final Rule on January 9, 2017.[24] The Agency did not accept any of PhRMA's proposals. The Final Rule, moreover, does not strike the last sentence of § 201.128, as FDA had proposed. Instead, the preamble explains that the Final Rule amends the regulation's last sentence to provide that "manufacturer knowledge may be relevant to intended use, but the Agency would not bring an enforcement action based *solely* on manufacturer knowledge that an approved/cleared product was being prescribed or used by doctors for an unapproved use. If there is other evidence of intended use, FDA may consider manufacturer knowledge as well as other evidence."[25] Under the amended regulation, FDA announced, "if the totality of the evidence establishes that a manufacturer objectively intends that a drug introduced into interstate commerce by him is to be used for [an unapproved use], he is required, in accordance with [the FDCA and FDA regulations], to provide for the drug adequate labeling that accords with such [unapproved use]."[26]

In response to PhRMA's comments regarding First Amendment protection for manufacturers' truthful and non-misleading communications with healthcare professionals about unapproved uses, FDA expressed disagreement "with the assertion that the current case law allows FDA to consider speech as evidence of intended use only when it is false or misleading."[27]

On February 7, 2017, FDA delayed the effective date of the Final Rule until March 21, 2017. The next day, MIWG, PhRMA, and BIO submitted their Petition to Stay and for Reconsideration of the Final Rule. On March 20, 2017, FDA issued the Request for Comments, further delaying the effective date of the Final Rule until March 19, 2018 and requesting comments on the issues raised in both the Final Rule and the Petition.[28]

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[23] *Id.*

[24] *See* 82 Fed. Reg. at 2193.

[25] *Id.*

[26] *Id.* at 2206.

[27] *Id.* at 2209.

[28] 82 Fed. Reg. 14319, 14320 (Mar. 20, 2017).

ANALYSIS

I. FDA Cannot Establish a Particular "Intended Use" Absent an External Claim or Statement by the Manufacturer About That Use

The concept of "intended use" has long been central to the federal government's regulation of pharmaceutical products. Since the early 20th century, federal law has defined a "drug" to include both the drugs listed in official compendia and also any other article "*intended for use* in the diagnosis, cure, mitigation, treatment, or prevention of disease."[29] If a particular article is "intended" to be used in such a manner, the article is a drug, meaning that it cannot be sold absent FDA approval and is otherwise subject to FDA regulation.

Beyond that, § 502(f)(1) of the FDCA provides that an FDA-approved drug is misbranded unless its labeling bears "adequate directions for use."[30] Although Congress exempted prescription drugs from this requirement of § 502(f)(1), an FDA regulation provides that a prescription drug is exempt from § 502(f)(1) *only* if the drug's labeling contains "adequate information" regarding any "use for which [the drug] *is intended*."[31] Because the FDCA bars manufacturers from changing the labeling of an approved drug to include "information" about an unapproved use, manufacturers are not exempt from § 502(f)(1), according to FDA's regulation. Similarly, because the FDCA does not permit manufacturers to amend a drug's labeling to include "directions" for an unapproved use, if an unapproved use is the manufacturer's "intended use," the drug is, under FDA's view, misbranded in violation of § 502(f)(1). The regulation at issue here—21 C.F.R. § 201.128—defines "intended use."

The Final Rule adopts an expansive standard for establishing "intended use" under § 201.128. FDA states it will consider the "totality of the evidence" and will rely on "any relevant source of evidence" to establish "intended use."[32] But neither common sense nor the relevant history and case law support such a broad approach. An article's intended use can be manifested only if the manufacturer conveys that intent to someone who is in a position to buy the article. The history and precedent confirm this commonsense understanding: in case after case, a particular "intended use" was established only where the manufacturer had made an external promotional claim about that use. Without such a limiting principle, FDA potentially could establish a product's "intended use" based solely on a manufacturer's internal business documents and communications, market conditions, draft FDA submissions, or clinical study

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[29] 21 U.S.C. § 321(g) (emphasis added); *see also* Pure Food and Drugs Act, ch. 3915, 34 Stat. 768, 769 (June 30, 1906) (likewise defining "drug" to include any "substance or mix of substances *intended to be used* for the cure, mitigation, or prevention of disease" (emphasis added)).

[30] 21 U.S.C. § 352(f)(1).

[31] 21 C.F.R. § 201.100(c)(1) (emphasis added).

[32] 82 Fed. Reg. at 2206, 2209.

protocols. That is overly broad and incorrect. As past court decisions and FDA enforcement actions illustrate, a particular "intended use" cannot be established absent, at a minimum, evidence that the drug manufacturer made an external claim about the relevant use.

In the Final Rule, FDA disagrees with commenters who urged FDA to "narrow the scope of evidence it will consider in determining intended use," contending that such narrowing would "not only create a loophole for manufacturers and distributors to evade FDA oversight of the marketing of approved/cleared medical products for unapproved uses but would also open the door to the marketing of wholly unapproved medical products—all to the detriment of the public health."[33] But PhRMA is not suggesting that FDA narrow the scope of evidence available to show "intended use" in a manner that would in any way harm public health. Instead, PhRMA believes that, at a minimum, a manufacturer must have made an external claim about a particular use before FDA can turn to other supporting evidence to establish that use as the manufacturer's "intended use."

PhRMA's proposed approach aligns with the body of judicial decisions adjudicating whether FDA properly established a particular "intended use" of a product. Importantly, we are not aware of any case in which a court has found that a product was intended for a particular use absent a manufacturer's external claim about that use. One court of appeals thus stated 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."[34]

In fact, courts consistently have *not* found evidence of "intended use" in the absence of external manufacturer claims. For example, the D.C. Circuit in *ASH v. Harris* explained 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 statutory interpretation."[35] The court did not find evidence of "intended use" in part because the petitioners were unable to show manufacturer intent through "objective evidence such as labeling, promotional material, and advertising."[36] In *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, Sigma-Tau Pharmaceuticals requested that FDA find that two generic manufacturers intended to sell a drug for an unapproved use solely by analyzing the "reality of the situation."[37] FDA declined to use the "reality of the situation" as evidence of intended use.[38] The court upheld FDA's decision declining to use surrounding circumstances as evidence of "intended use," citing its own statement in *Brown & Williamson Tobacco Corp. v. FDA* that "no court has ever found a product

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[33] *Id.* at 2207.

[34] *Brown & Williamson Tobacco Corp. v. FDA*, 153 F. 3d 155, 163 (4th Cir. 1998) (affirming district court's decision that tobacco manufacturers did not intend for tobacco to be used as a drug) (internal quotation marks omitted), *aff'd*, 529 U.S. 120 (2000).

[35] 655 F.2d 236, 238-39 (D.C. Cir. 1980) (emphasis added).

[36] *Id.* at 239.

[37] *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141, 147 (4th Cir. 2002).

[38] *Id.* at 145.

is 'intended for use' or 'intended to affect' within the meaning of the [FDCA] absent manufacturer claims as to that product's use."[39]

To our knowledge, in all cases where courts have found a new "intended use," they have done so, at least in part, based on an external claim about that use. For example, in 1920 the court in *Bradley v. United States* found that the plaintiff violated the Pure Food and Drug Act for shipping bottles of water in interstate commerce with a label on the bottles that stated the following: "Recommended in the treatment of Bright's Disease, Diabetes, Dropsy, Cystitis, Gout, Rheumatism, Indigestion, Kidney and Bladder troubles."[40] The court held that this label was false and misleading, and that the label represented a claim that the water would cure, or at least alleviate, the mentioned diseases. The court accordingly held that the manufacturer of the water intended that it be used as a drug and that the manufacturer was therefore shipping a misbranded product in interstate commerce.[41] Similarly, the court in *United States v. 46 Cartons, More or Less, Containing Fairfax Cigarettes* found that the manufacturer's cigarettes fell within the definition of a drug because of the false and misleading external representations made by the manufacturer. The court explained that the manufacturer sold the cigarettes with a circular stating that the cigarettes were "effective in preventing respiratory diseases, common cold, influenza, pneumonia, acute sinusitis, meningitis, tuberculosis, [and a host of other diseases] . . . [and] that the smoking of these cigarettes is innocuous for persons suffering from circulatory diseases, high blood pressure and various heart conditions."[42] The court went on to quote the legislative history of FDCA: "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."[43] Therefore, due to the false and misleading external manufacturer claim, the court held that the manufacturer intended for the cigarettes to be used as a drug, and that the product was therefore misbranded under the FDCA.[44]

More recently, the court in *American Health Products Co., Inc. v. Hayes* held that a "starchblockers" product was a drug, reasoning that "the courts have always read the clauses in the statutory definitions employing the term 'intended' to refer to *specific marketing representations*," and that Congress wanted the definition of a drug "to cover products *marketed*

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[39] *Id.* at 147 (citations omitted).

[40] 264 F. 79, 80 (5th Cir. 1920). Prior to the passage of the Federal Food, Drug, and Cosmetic Act in 1938, the Pure Food and Drugs Act of 1906, in a manner similar to the current intended use statute, defined "drug" as "any substance or mixture of substances intended to be used for the cure, mitigation, or prevention of disease of either man or other animals."

[41] *Id.* at 82; *see also Goodwin v. United States*, 2 F.2d 200 (6th Cir. 1924) (holding that cases of water shipped in interstate commerce were "intended for use" as a drug because they were falsely labeled as beneficial for "a long list of ailments" and as having "healing powers" and being a "reliable remedy").

[42] 113 F. Supp. 336, 337 (D.N.J. 1953).

[43] *Id.* at 338 (quoting Senate Report No. 361, 74th Cong., 1st Session from the Committee on Commerce Report to accompany S. 5) (emphasis added).

[44] *Id.* at 339.

for their physiological effects."[45] The plaintiffs in that case had marketed their product to aid weight reduction—*i.e.*, a claim that the product was "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals" within the FDCA's definition of a "drug." Therefore, although the plaintiffs claimed the product was a food, the manufacturer's external claims about the product led the court to conclude that the product was a drug, given the "intended use" for which it was marketed.[46]

In accordance with these precedents, an article's "intended use" cannot be established absent, at a minimum, an external claim by the manufacturer about that use. We therefore urge FDA to amend 21 C.F.R. § 201.128 to confirm that knowledge alone is insufficient to establish an "intended use" of a drug and that an external manufacturer claim is required to establish an "intended use." We further urge FDA to reject the overly expansive "totality of the evidence" standard for establishing an "intended use" set forth in the Final Rule. The broad "totality of the evidence" standard that FDA has proposed could impermissibly result in an "intended use" based on strictly internal evidence, wholly circumstantial or inconclusive evidence not tied to the dissemination of the article, or, as explained below, First Amendment-protected communications.

II. Overly Restrictive Regulation of Manufacturers' Truthful and Non-Misleading Communications with Healthcare Professionals About Unapproved Uses of FDA-Approved Drugs Violates the First and Fifth Amendments

As described above, the Proposed Rule asserted that FDA may consider as evidence of intended use "*any* claim or statement by or on behalf of a manufacturer that explicitly or implicitly proposed a product for a particular use."[47] In response, PhRMA's comments on the Proposed Rule explained that the First Amendment precludes FDA from bringing an enforcement action for misbranding based on a manufacturer's truthful and non-misleading communications with healthcare professionals about an unapproved use of an FDA-approved drug. But the Final Rule reiterates the view that FDA may consider "*any* claim or statement" by a manufacturer. In response to First Amendment concerns, the Final Rule provides that FDA "does not agree with the assertion that the current case law allows FDA to consider speech as evidence of intended use only when it is false or misleading."[48] In this respect, FDA has misconstrued the current case law.[49]

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[45] 574 F. Supp. 1498, 1505 (S.D.N.Y. 1983) (internal quotation marks omitted) (emphasis added).

[46] *Id.* at 1510.

[47] 82 Fed. Reg. at 2195 (emphasis added).

[48] *Id.* at 2193, 2209.

[49] PhRMA acknowledges that FDA recognizes that there is some speech, such as manufacturers responding to unsolicited requests for information and sharing reprints of scientific or medical journal articles, that should not be used as evidence of intended use. 82 Fed. Reg. at 2210. The

Footnote continued on next page

As the Supreme Court reaffirmed in *Sorrell v. IMS Health Inc.*, "[s]peech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment."[50] The First Amendment serves a particularly critical function "in the fields of medicine and public health, where information can save lives."[51]

In *Sorrell*, the Supreme Court applied "heightened judicial scrutiny" to strike down a Vermont law that burdened pharmaceutical manufacturers' communications with healthcare professionals about their medicines because the law imposed both "content- and speaker-based restrictions" on protected speech.[52] The Vermont law had "disfavor[ed] marketing, that is, speech with a particular content," and had "disfavor[ed] specific speakers, namely pharmaceutical manufacturers."[53] The Court in *Reed v. Town of Gilbert* subsequently reiterated that "[c]ontent-based laws—those that target speech based on its communicative content—are presumptively unconstitutional and may be justified only if the government proves that they are narrowly tailored to serve compelling state interests."[54] In this term, the Supreme Court in *Matal v. Tam* struck down the disparagement clause of the Lanham Act, which prevents the Patent and Trademark Office from granting trademark applications that "disparage" any "persons," because the disparagement clause violates the First Amendment.[55] Notably, in the opinion, a four-justice concurrence reiterated that viewpoint-based discrimination invokes heightened judicial scrutiny, even when commercial speech is at issue.[56] In addition, one justice went further, reasoning that the *Central Hudson* test applicable to commercial speech should be overruled and that all speech restrictions should be subject to heightened scrutiny.[57]

Following *Sorrell*, the Second Circuit in *United States v. Caronia* held that "[t]he government's construction of the FDCA's misbranding provisions to prohibit and criminalize the promotion of off-label drug use by pharmaceutical manufacturers is content- and speaker-based,

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current submission addresses proactive manufacturer communications other than dissemination of reprints.

[50] 564 U.S. 552, 557 (2011).

[51] *Id.* at 566.

[52] *Id.* at 563, 565.

[53] *Id.* at 564.

[54] 135 S. Ct. 2218, 2226-27 (2015) ("Government regulation of speech is content based if a law applies to particular speech because of the topic discussed or the message expressed." (citing *Sorrell*, 564 U.S. at 563)).

[55] *Matal v. Tam*, 137 S.Ct. 1744, 1748 (2017).

[56] 137 S.Ct. at 1750 (8-0 decision) (Kennedy, J., concurring) (citing *Sorrell*, 562 U.S. at 566, for the idea that the test for discrimination based on viewpoint "requires heightened scrutiny whenever the government creates regulation of speech because of disagreement with the message it conveys.").

[57] 137 S.Ct. at 1769 (Thomas, J., concurring).

and, therefore, subject to heightened scrutiny."[58] *Caronia* further concluded that a misbranding conviction based solely on a pharmaceutical sales representative's truthful and non-misleading speech about an unapproved use would fail First Amendment scrutiny even under the *Central Hudson* test. Because "physicians can prescribe, and patients can use" FDA-approved drugs for unapproved uses, the court explained, restrictions on manufacturers' speech about such uses would not "directly further the government's goals."[59] The court further reasoned that such a restriction "'paternalistically' interferes with the ability of physicians and patients to receive potentially relevant treatment information" and "could inhibit, to the public's detriment, informed and intelligent treatment decisions."[60]

The paternalism criticized in *Caronia* has long been regarded as an insufficient—and, indeed, illegitimate—justification for restricting truthful speech.[61]

Applying *Sorrell* and *Caronia* here, enforcement actions for misbranding based on manufacturers' truthful and non-misleading communications with healthcare professionals about unapproved uses trigger heightened judicial scrutiny, and fail that standard. Even under the *Central Hudson* test, overly restrictive FDA regulation of manufacturers' truthful and non-misleading speech would fail First Amendment scrutiny.[62] FDA generally would not be able to establish that restrictions on truthful and non-misleading manufacturer speech directly advance a substantial government interest that is not more extensive than necessary.[63]

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[58] *United States v. Caronia*, 703 F.3d 149, 164–65 (2d Cir. 2012).

[59] 703 F.3d at 166.

[60] *Id.*

[61] *See, e.g.*, *44 Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 503 (1996) ("[B]ans against truthful, non-misleading commercial speech . . . usually rest solely on the offensive assumption that the public will respond 'irrationally' to the truth. The First Amendment directs us to be especially skeptical of regulations that seek to keep people in the dark for what the government perceives to be their own good." (quoting *Linmark Assocs., Inc. v. Willingboro Twp.*, 431 U.S. 85, 96 (1977))); *Va. State Bd. of Pharm. v. Va. Citizens Consumer Council, Inc.*, 425 U.S. 748, 770 (1976) (criticizing government's "highly paternalistic approach" to free flow of truthful, non-misleading information about pharmaceutical products).

[62] PhRMA recognizes that patent protection and periods of non-patent exclusivity are critical to incentivizing investment in research and development of new uses, and that preserving these incentives is critically important. *See* PhRMA, Comment to Docket No. FDA-2016-N-1149, 24-27 (Apr. 19, 2017). In its First Amendment Memorandum, FDA agreed that protecting innovation incentives serves an important regulatory interest for purposes of First Amendment analysis. *See* First Amendment Memorandum, at 15-16. As PhRMA explained in its above-cited comment letter, PhRMA agrees that FDA may restrict truthful and non-misleading speech consistent with First Amendment precedent where allowing the communication to occur would negate or dilute a manufacturer's data or marketing exclusivity rights.

[63] *See Cent. Hudson*, 447 U.S. at 557; *Thompson v. W. States Med. Ctr.*, 535 U.S. 357 (2002) (striking down federal statute prohibiting pharmacy compounding advertising under *Central Hudson* commercial speech test); *Va. State Bd. of Pharmacy*, 425 U.S. at 773 (striking down state statute prohibiting pharmacy advertising of prescription drug prices).

Relying on *Wisconsin v. Mitchell*[64] and *Whitaker v. Thompson*,[65] the Final Rule asserts that "[t]he First Amendment . . . does not prohibit the evidentiary use of speech to establish the elements of a crime or to prove motive or intent.'"[66] But as FDA itself notes in the Final Rule,[67] the district court in *Amarin Pharma, Inc. v. FDA* rejected this exact argument by the Agency.[68] Following *Caronia*, the court in *Amarin* held: "Where the speech at issue consists of truthful and non-misleading speech promoting the off-label use of an FDA-approved drug, such speech, under *Caronia*, cannot be the act upon which an action for misbranding is based."[69] The court rejected FDA's argument—repeated in the Final Rule—that the government may use speech "as evidence of intent."[70] As the court explained, "the proposition that speech can be admissible in evidence to prove intent or motive in a criminal case is beside the point here," because FDA's restrictions on manufacturer communications about unapproved uses "take[] aim at truthful, non-misleading speech," and not any other "*actus reus*."[71] This case is thus distinguishable from *Wisconsin v. Mitchell* and *Whitaker v. Thompson*, where speech was introduced as evidence of intent to support a separate, independently illegal act. With respect to truthful and non-misleading communications about unapproved uses of medical products, there is no illegal act other than speech.

Contrary to FDA's undeveloped assertion in the Final Rule,[72] dicta in *United States ex rel. Polansky v. Pfizer, Inc.*[73] does not revive the failed argument that FDA may use truthful and non-misleading speech about an unapproved use as "evidence of intent" in a criminal or civil enforcement action alleging misbranding. *Polansky* affirmed the dismissal of a relator's False Claims Act claims against a pharmaceutical manufacturer on the ground that an FDA-approved drug's labeling did not purport to require compliance with certain national treatment guidelines.[74] In a footnote discussing an issue not material to that outcome, the Second Circuit recognized that the government may not, consistent with the First Amendment, restrict "'the simple promotion of a drug's off-label use' . . . where the promotional speech is not false or

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[64] 508 U.S. 476 (1993).

[65] 353 F.3d 947 (D.C. Cir. 2004).

[66] 82 Fed. Reg. at 2209 (internal quotations omitted).

[67] *Id.*

[68] 119 F. Supp. 3d 196, 226 (S.D.N.Y. 2015).

[69] *Id.*

[70] *Id.* at 228.

[71] *Id.* at 227-28.

[72] 82 Fed. Reg. at 2209.

[73] 822 F.3d 613 (2d Cir. 2016).

[74] *Id.* at 618.

misleading."[75] That is precisely what FDA's regulations do in broadly restricting truthful and non-misleading manufacturer communications about unapproved uses.

The Final Rule further asserts that FDA's "public health interests" justify the restrictions on speech under *Central Hudson*.[76] But, as PhRMA explained in its comments responding to FDA's notification of public hearing and First Amendment Memorandum—which describe precisely the same public health interests—FDA's restrictions on truthful and non-misleading manufacturer communications restrict far more speech than necessary.[77] A modified regulatory approach, guided by the PhRMA-BIO Principles, would adequately preserve FDA's legitimate interests without infringing the First Amendment rights of pharmaceutical manufacturers.

Additionally, FDA's argument that *Caronia* is no longer good law—or that the Second Circuit might reconsider its decision—in light of a single Canadian study about "unapproved uses and adverse drug events,"[78] is meritless.[79] The Canadian study, which showed "an association between unapproved uses and adverse drug events," noted that "[t]he rate of [Adverse Drug Events ('ADEs')] for off-label use (19.7 per 10,000 person-months) was higher than that for on-label use (12.5 per 10,000 person-months)." Nevertheless, the study also found that "off-label use with strong scientific evidence has the same risk for ADEs as on-label use." Therefore, although the authors of the Canadian study appropriately illustrated the value of scientifically sound information, they mischaracterized the value of speech regarding unapproved uses. In citing the Canadian study, FDA ignores that that the Second Circuit did not reason that unapproved uses never lead to adverse drug events, but rather that such uses are lawful and therefore may be discussed truthfully by pharmaceutical manufacturers and others alike. And, in any event, the safeguards incorporated into the PhRMA-BIO Principles—scientifically and statistically sound methodologies, disclosure of contextual information, and audience sophistication—all help to ensure that communications are truthful and non-misleading as a matter of scientific merit and sound policy.

Finally, the Due Process Clause of the Fifth Amendment requires that FDA ensure that the definition of "intended use" is sufficiently clear and unambiguous so that manufacturers receive "fair notice of what is prohibited."[80] Where a law has the capacity to chill constitutionally protected activity, especially speech protected by the First Amendment, the law raises even greater constitutional concerns. It is well recognized that "where a vague statute abuts upon sensitive areas of basic First Amendment freedoms, it operates to inhibit the exercise

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[75] *Id.* at 615 n.2 (quoting *Caronia*, 703 F.3d at 160).

[76] 82 Fed. Reg. at 2209-2210.

[77] *See* PhRMA, Comment to Docket No. FDA-2016-N-1149, 13-27 (Apr. 19, 2017).

[78] *See* 82 Fed. Reg. at 2210 (discussing Tewodros Eguale et al., Association of Off-Label Drug Use & Adverse Drug Events in an Adult Population, 176 JAMA INTERN. MED. 55 (2016)).

[79] Eguale, et al., *supra* note 78, at 55.

[80] *FCC v. Fox Television Stations, Inc.*, 132 S. Ct. 2307, 2317-18 (2012).

of those freedoms."[81] "When speech is involved, rigorous adherence to [due process] requirements is necessary to ensure that ambiguity does not chill protected speech."[82] To comport with due process principles, FDA must more clearly define the types of speech that may be used as evidence of intended use.

CONCLUSION

PhRMA appreciates the opportunity to comment on the important issues raised by the Final Rule and MIWG, PhRMA, and BIO's Petition to Stay. For the reasons described, we believe that the FDCA, its history, and relevant precedent require that to establish an article's "intended use," there must be an external manufacturer claim about that use. Furthermore, enforcement actions based on manufacturers' truthful and non-misleading communications with healthcare professionals about unapproved uses generally violate the First Amendment, absent intellectual property considerations not pertinent here. We urge FDA to amend its "intended use" regulations accordingly, and to align its regulations more generally to the PhRMA-BIO Principles. PhRMA values its relationship with FDA, and looks forward to continuing to work with FDA on these important matters.

Respectfully submitted,

_____/x/_____	_____/x/_____
James C. Stansel	Kelly F. Goldberg
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[81] *Grayned v. City of Rockford*, 408 U.S. 104, 108 (1972).

[82] *Fox*, 132 S. Ct. at 2317.

Appendix A

Principles on Responsible Sharing of Truthful and Non-Misleading Information About Medicines with Health Care Professionals and Payers

PRINCIPLES ON RESPONSIBLE SHARING OF TRUTHFUL AND NON-MISLEADING INFORMATION ABOUT MEDICINES WITH HEALTH CARE PROFESSIONALS AND PAYERS

INTRODUCTION

In the era of data-driven medicine, where all parties seek more, not less, information about the safety, effectiveness, and value of treatments, fostering informed communications among all stakeholders is critical. Today, the wealth of information about medicines is more comprehensive and complex than ever before. Scientific knowledge and new findings go far beyond data sets produced from clinical trials, often are outside the scope of the parameters established by Food and Drug Administration (FDA) regulations, and often outdate the FDA-approved labeling. In addition to information in the approved labeling for medicines, biopharmaceutical companies continually generate and collect important data and analyses that can benefit patient care and enhance the efficiency of our health care system.

To exercise sound medical judgment in treating patients, health care professionals must understand the full range of treatment options, including both established and emerging information about available medications. Biopharmaceutical companies are uniquely positioned to help health care professionals achieve the best outcomes for patients, because companies can provide timely, accurate, and comprehensive information about both approved and unapproved uses of the medications they research, develop, and bring to patients. PhRMA, BIO and their members believe that the availability of a wider range of truthful and non-misleading information can help health care professionals and payers make better informed medical decisions for their patients, which in turn will benefit patients.

In order to support the best use of scientific information for patient care, PhRMA and BIO endorse these Principles on Responsible Sharing of Truthful and Non-Misleading Information About Medicines with Health Care Professionals and Payers. These Principles are intended to form the basis for defining new and clear regulatory standards governing responsible, truthful and non-misleading communications to inform health care professionals about the safe and effective use of medicines. The Principles pertain primarily to data and information outside of FDA-approved labeling, and are intended to establish responsible, science-based parameters for accurate and trusted information sharing.

KEY CONCEPTS OF THE PRINCIPLES INCLUDE OUR MEMBERS':

- **Commitment to Science-based Communication.** Communications should be based on analyses using scientifically- and statistically-sound methodologies. There are many types of data and analyses that are scientifically- and statistically-sound, and thus can support truthful and non-misleading communication about medicines. These include analyses that can improve patient care based on pharmacoeconomics, usage based on real world evidence, and post hoc analyses that focus on specific sub-populations.

- **Commitment to Provide Appropriate Context about Data.** Communications should clearly disclose appropriate contextual information about the data presented, including information about limitations of the data and the analyses conducted to prevent health care professionals and payers from reaching inaccurate conclusions or forming misimpressions about the efficacy or safety of a medicine.

- **Commitment to Accurate Representation of Data.** Limitations on communications should be based principally on ensuring that data are represented accurately, which includes disclosing limitations of the data and the scientific and analytical methodologies used. Communications and underlying information can be truthful and non-misleading without regard to the identity of the speaker.

Finally, robust scientific discourse is critical to scientific progress and advances in public health. Current law fosters scientific discourse and debate in various settings, such as scientific presentations or other scientific communications during major medical association conferences and publication of peer-reviewed scientific and medical journal articles. These forms of scientific communications fall outside of the FDA's oversight, and the Principles described here do not apply to them.

PRINCIPLES:

1. **Commitment to Accurate, Science-Based Communications**
   Biopharmaceutical companies should communicate accurate information based on established medical and scientific methodologies. Companies should not share information unless it is based on scientifically- and statistically-sound methodologies.

   SCENARIO 5 IN APPENDIX B ILLUSTRATES THIS PRINCIPLE.

2. **FDA-Approved Labeling is a Primary Source in Sharing Information with Health Care Professionals About Medicines**
   Communications about a medicine are truthful and non-misleading if they accurately and fairly describe information contained in its FDA-approved labeling. Companies should continue to use the FDA-approved labeling as a primary source in communicating to health care professionals about approved medicines. In communicating information from the FDA-approved labeling, companies must fairly describe both the efficacy and the safety profile of the medication, including important risks.

   SCENARIO 14 IN APPENDIX B ILLUSTRATES THIS PRINCIPLE.

3. **Companies Should Provide Scientific Substantiation if Shared Information is Not Contained in FDA-Approved Labeling**
   Health care professionals rely on a wide range of data from a variety of sources to inform patient care. There are many types of data and analyses that are scientifically- and statistically-sound, and thus can support truthful and non-misleading communication about medicines. When communicating evidence based on clinical research other than in the form of adequate and well-controlled trials, companies should disclose sufficient information for the audience to understand the specific research and any limitations. It is particularly important for a company to portray accurately the applicable methodologies and data, which can include limitations in the study methodology and/or statistical results.

   To help ensure that physicians and other trained health care professionals can appropriately weigh data that are not contained in the FDA-approved labeling for a drug, companies should make appropriate disclosures, including the following:

   - The design and implementation of the study (including the patient populations included and excluded, the total number of patients evaluated, the length of the study, the primary and key secondary endpoints, and whether the study met those endpoints);
   - Significant limits on the study methodology (e.g., whether and how the study methodology may be subject to potential sources of bias or other weaknesses);
   - The statistical analysis plan;
   - Limitations of the statistical results (e.g., the statistical significance of the data and whether the results can be generalized); and
   - Other relevant evidence that is necessary to an informed medical judgment, including peer-reviewed contrary evidence.

   Companies should disclose information as part of the oral or written communication sufficient to ensure that the communication is not misleading, and may direct health care professionals to a website or other source for more comprehensive information.[1]

   SCENARIOS 1 AND 2 IN APPENDIX B ILLUSTRATE THIS PRINCIPLE.

4. **Additional Science-based Information from Sources Other Than FDA-Approved Labeling Helps Health Care Professionals and Payers Make Informed Decisions for Patients**
   PhRMA, BIO and their members believe that the availability of a wider range of truthful and non-misleading information can help health care professionals and payers make better informed medical decisions for their patients, which in turn will benefit patients. Sources for such additional information include:

[1] Such information may be password-protected to ensure that it may be accessed only by health care professionals.

- Data from randomized, controlled clinical trials;
- Pharmacoeconomic information;
- Post hoc analyses of clinical trial results, including sub-population analyses;
- Observational data and real world evidence; and
- Physician treatment guidelines[2]

PhRMA, BIO and their members can and should be able to communicate truthful and non-misleading information from these additional sources in a responsible manner. To ensure that health care professionals are able to make informed judgments based on the information provided, it may be necessary for the company to include a variety of disclosures and disclaimers. Therefore, when communicating information not in the FDA-approved labeling, companies should include contextual information that allows health care professionals fully and fairly to assess the significance of, and any limitations upon, the evidence presented.[3] The contextual information provided by a company to ensure that a communication is truthful and non-misleading will vary based on several factors, including:

- The complexity of the information presented;
- The underlying scientific research supporting it;
- The existence of other research reaching different results; and
- The sophistication of the audience;

SCENARIOS 1-4 AND 7 IN APPENDIX B ILLUSTRATE THIS PRINCIPLE.

5. Communications Should Be Tailored to the Sophistication of the Intended Audience

To communicate information in a truthful and non-misleading manner, biopharmaceutical companies should carefully consider the level of sophistication of the intended audience. For example, the training and experience regarding the subject addressed in the communication may vary among different types of health care professionals (e.g. ranging from general practitioners to health care professionals who work for payers and routinely review pharmacoeconomic analyses). Companies can and should determine the sophistication of the health care professionals who receive the companies' communications. Companies can and should tailor their communications based on that determination, providing more detailed contextual information for audiences that require additional background to evaluate the relevance and significance of the information presented.

SCENARIO 10 IN APPENDIX B ILLUSTRATES THIS PRINCIPLE.

6. Science-based Information About Alternative Uses of Medicines Can Improve Health Care Decision-Making

There exists a wealth of important information about the approved uses of medicines. In addition, respected third-parties, such as national medical associations and compendia services, often publish compendia or treatment guidelines that recommend or describe uses of medicines to treat patients outside the FDA-approved labeling. Recognizing the public health value of such alternative uses of approved medicines, public and private insurers often reimburse for them, and an estimated 21 percent of prescriptions by health care professionals are for alternative uses of approved medicines.

Biopharmaceutical companies are expected to collect the most comprehensive and up-to-date clinical information about their medicines—including information on alternative uses beyond the approved indication or dosing. Because this information can help health care professionals make informed decisions about the best treatments for their patients, companies should be able to communicate about such medically accepted alternative uses in a truthful and non-misleading manner.

[2] Several of these sources of information are described in greater detail in Appendix A.

[3] Biopharmaceutical companies should not be hesitant to publish new scientific developments; however, publication should not be a prerequisite to truthful and non-misleading communications about such new developments.

Furthermore, companies must be able to participate fairly in the medical and policy discourse about the appropriate use of their medicines – even if communications include information outside of the FDA-approved labeling. This is especially true when other stakeholders conduct research about a company's product and communicate about it publicly. In such instances, the company should be able to respond in a truthful and non-misleading manner.

As with any other type of information not included in FDA-approved labeling, company communications about alternative uses of medicines should disclose sufficient information to permit health care providers to assess the significance of, and limitations on, the evidence supporting such alternative uses. When communicating about alternative uses of medicines to appropriately sophisticated audiences, companies should disclose, among other things:

- The regulatory status of the medicine (e.g., FDA-approved, FDA-approved for another use, not FDA-approved);
- The underlying scientific research supporting such alternative uses (e.g., one or more adequate and well-controlled clinical trials, scientifically-sound post hoc analyses of clinical trial results (including sub-population analysis), open label extensions of clinical trials, registration studies, real-world evidence, etc.);
- Limitations on study methodologies and resulting data; and
- The relevant evidence that is necessary to an informed medical judgment, including peer-reviewed contrary evidence.

Companies should include these disclosures with the oral or written communications.

SCENARIOS 6, 7, AND 8 IN APPENDIX B ILLUSTRATE THIS PRINCIPLE.

7. Communicating with Payers About New Medicines and New Uses of Approved Medicines Facilitates Patient Access Upon Approval

Prompt access to new medicines, or to approved medicines with new indications, can be critical to patient care. This is particularly true when the new medicine or new indication is a breakthrough in treating a life-threatening disease or where the new drug is safer or more effective than existing treatment. Therefore, biopharmaceutical companies should be able to communicate certain information to insurance providers, pharmacy benefit managers and government health care programs, so they may consider whether to reimburse for the medicine and account for the potential cost of the new medicine. For example, a company should be able to describe the company's research and development pipeline, the status of any FDA applications, the anticipated use(s) of the company's pipeline products, relevant data from the clinical trials, applicable treatment guidelines, and pharmacoeconomic information. Any such description should make clear that the FDA has not yet approved the drug, the particular use, or the information being conveyed.

SCENARIOS 9, 10 , AND 11 IN APPENDIX B ILLUSTRATE THIS PRINCIPLE.

8. Real-World Evidence Based on Patient Experience and Pharmacoeconomic Information Can Improve Understanding of Health Outcomes and Costs

Many health care organizations, including insurance providers, managed care organizations, pharmacy benefit managers, government health care programs, hospital systems, accountable care organizations, and integrated delivery networks make decisions on health care delivery across large populations. These organizations possess patient data relating to real-world uses of approved medicines, conduct their own research on such data, and may wish to collaborate with biopharmaceutical companies to determine the overall impact of medicines in specific patient populations. Real-world evidence—evidence derived from data gathered from actual patient experiences—can help improve our understanding of disease and health.[4] For example, modeling long-term endpoints and effects on different populations can help payers and health systems understand expected benefits for patients.

So long as the research methods are sound and well-described, companies should be able to communicate truthful and non-misleading

[4] See Robert M. Califf & Rachel Sherman, What We Mean When We Talk About Data (Dec. 10, 2015), available at http://blogs.fda.gov/fdavoice/index.php/2015/12/what-we-mean-when-we-talk-about-data/?source=govdelivery&utm_medium=email&utm_source=govdelivery.

information about analyses of real world data with payers and health systems. These organizations are very sophisticated about such analyses and can evaluate the significance and limitations of the results.

SCENARIO 12 IN APPENDIX B ILLUSTRATES THIS PRINCIPLE.

9. Commitment to Share Information Published in Scientific or Medical Journals

FDA has recognized that sharing reprints of peer-reviewed scientific or medical journal articles reporting clinical research about alternative uses of approved drugs serves important public health and policy goals. FDA therefore has issued recommendations concerning "Good Reprints Practices" permitting dissemination of peer-reviewed reprints to health care professionals. PhRMA, BIO and its members support FDA's continued focus on providing concrete guidance regarding the types of disclosures and other steps manufacturers should take to disseminate information about unapproved uses without risking regulatory or even criminal enforcement. Nevertheless, certain of FDA's recommended practices would restrict truthful and non-misleading communication with health care professionals and ultimately risk delaying the provision of timely, educational, and accurate information to health care professionals about certain unapproved uses, many of which are medically accepted and indeed even the standard of care for certain diseases. For example, biopharmaceutical companies should be able to share journal articles about research that they sponsor about their own medications as well as reprints of research sponsored by others.

The same public health and policy justifications set forth in the Good Reprint Practices also apply to oral or written summaries of such reprints. Therefore, in addition to disseminating reprints, company representatives should be able to describe information presented in such reprints. To help ensure that physicians and other trained health care professionals can appropriately weigh such oral or written summaries of data contained in a medical or scientific reprint, companies should include appropriate disclosures, including the following:

- Accurate and balanced information about the approved product labeling (including the indication, limitations of use, efficacy and safety data described therein);
- The type of research that is the subject of the reprint (including the study design, method of analysis, and appropriate, context-specific disclosures regarding the limitations with retrospective meta-analysis);
- The results reported in the reprint, including the statistical significance and confidence intervals of each result;
- Information about the source of funding for the reprint; and
- Other relevant evidence that is necessary to an informed medical judgment, including peer-reviewed contrary evidence.

SCENARIO 13 IN APPENDIX B ILLUSTRATES THIS PRINCIPLE.

[5] The company should disclose the trial design and analytical methodology used in the study, including any limitations of the methodology. The company should not simply direct the health care professional to the reprint for a description of the study design and analytical methodology.

APPENDIX A

TYPES OF INFORMATION ABOUT MEDICINES

In addition to information contained in the FDA-approved labeling for medicines, biopharmaceutical companies continually generate and collect the following types of information about medicines. Responsible sharing of information, including the following categories, can improve patient care and the efficiency of the health care system:

- **Data from randomized, controlled clinical trials** – Scientifically rigorous and FDA-regulated clinical studies, including Phase I - IV clinical trials, evaluate pre-specified endpoints under a clearly defined analysis plan. Clinical trials are among the most reliable tools in evaluating the safety and effectiveness of medicines. The results often are independently peer-reviewed and published; however, only a fraction of the data from these studies is contained in the FDA-approved labeling.

- **Post hoc analyses, including sub-population data** – Randomized controlled clinical trials and observational studies often collect information on the safety and effectiveness of medicines in subpopulations, including specific gender and ethnic cohorts. The analysis of these data often occurs after the conclusion of the trial, as the subpopulation data may not have been pre-specified end-points or part of the original plan of analysis. If the trial has met its primary endpoint, this specific sub-population information can help health care professionals develop treatment strategies based on more precise safety and efficacy data for a particular cohort of patients.

- **Observational data and real-world evidence** – A growing amount of information is gathered from claims data, electronic medical records, or patient registries that can provide specific and up-to-date information about the actual use of approved medicines. Observational data, comparative effectiveness research, and other real-world evidence can help clinicians understand how medicines perform across a diverse patient population outside of controlled trials. Such data may reflect prescribing patterns in different clinical practice settings, alternative doses, and differing durations of treatment, as well as comparisons between two or more therapies.

- **Pharmacoeconomic information** – Health care economic data demonstrating the value of medicines can be obtained from clinical trials, observational studies, reviews of medical record databases, or other predictive modeling techniques. This information can include analyses of outcomes from patient population data sets, cost-effectiveness models, and budget models. Such information can help improve the efficiency of patient care and of the health care system, as well as better inform payers regarding the budget implications of coverage decisions.

APPENDIX B

EXAMPLES OF RESPONSIBLE SHARING OF TRUTHFUL AND NON-MISLEADING INFORMATION IN VARIOUS COMMUNICATION SETTINGS

The following hypothetical scenarios are meant to illustrate how companies may apply the Principles described in this document under new regulatory standards governing responsible information sharing with health care professionals. These scenarios demonstrate that responsible sharing of truthful and non-misleading information is highly fact-specific.

Scenario 1: After receiving approval for a drug indicated for the reduction of chemotherapy-induced nausea, a biopharmaceutical company conducts a Phase IV randomized, controlled clinical trial using pre-specified clinical endpoints to evaluate the average duration of efficacy for the approved course of therapy. This is a new efficacy measure, not included in the FDA-approved labeling. The study meets its primary and secondary endpoints. FDA has not expressed views on the study, and the company has not sought to include the new data in the labeling. No randomized, controlled studies conflict with this study. To communicate the results of this trial to prescribing physicians in a truthful and non-misleading manner, the company should disclose, among other things, (a) the study design (including the number of patients in each study arm, the inclusion and exclusion criteria, the pre-specified primary and key secondary endpoints, and whether the study met those endpoints) and the statistical significance and confidence interval of the results on the key endpoints; (b) pertinent safety results; (c) that the information is based on only one randomized, controlled trial; and (d) that the study is not included in the product's package insert and that FDA did not consider it in approving the product. The company should summarize these disclosures in the oral or written communications, and can refer the health care professional to a website for more comprehensive information about the study. This scenario implicates Principles 3 and 4.

Scenario 2: After receiving approval for a drug's use in adult patients, a biopharmaceutical company submits a supplemental NDA for an additional use in children. The company conducts a randomized, controlled clinical trial on the second use, and the study meets the pre-specified endpoints. FDA acknowledges that the clinical trial demonstrated the safety and efficacy of the drug in the tested population, but there will be a delay with an update to the approved labeling addressing these additional data. Another study conducted by independent investigators presents contrary evidence about the efficacy of the drug in children. To communicate the results of the trial it conducted to prescribing physicians in a truthful and non-misleading manner before the FDA approves updated labeling, the company should disclose, among other things: (a) the study design, number of patients studied, and key exclusion criteria; (b) the results of the pre-specified primary and key secondary endpoints (including p values and confidence intervals); (c) pertinent safety results; (d) the existence of only one randomized, controlled trial supporting the information; (e) the lack of any reference to the study in the labeling; (f) regulatory status; and (g) other evidence that is necessary to an informed medical judgment, including peer-reviewed contrary evidence (including p values and confidence intervals). The company should summarize these disclosures in the oral or written communications, and can refer the health care professional to a website for more comprehensive information about the study. This scenario implicates Principles 3 and 4.

Scenario 3: A drug for treating allergic rhinitis receives FDA approval based on a composite efficacy endpoint that measured patients' total symptom improvement over six individual symptoms. The three pivotal clinical studies that formed the basis for approval measured efficacy in the individual symptoms as tertiary endpoints. The efficacy results for four of the six individual symptoms were statistically significant. Because the studies did not designate individual symptom scores as secondary endpoints, FDA does not permit the manufacturer to include these data in the labeling, but has not otherwise expressed views on these results. To communicate this information to prescribing physicians in a truthful and non-misleading manner, the company should disclose, among other things: (a) the number of patients studied, as well as the p values and confidence intervals for all six of the symptoms evaluated; (b) the omission of individual symptom efficacy as a primary or secondary end point of the study;

(c) the prospective definition of and pre-specified analysis plan for these tertiary endpoints; (d) the inclusion or absence of a prospectively planned adjustment to control for false positives or other forms of potential bias; (e) any other risk of potential bias regarding this data; (f) pertinent safety results; and (g) FDA's decision not to include this data in the product labeling and the reasons why. The company should summarize these disclosures in the oral or written communications, and can refer the health care professional to a website for more comprehensive information about the study. This scenario implicates Principle 4.

Scenario 4: A biopharmaceutical company manufactures a drug approved for treating symptoms of Parkinson's disease in adults. The company conducts a methodologically sound, post hoc analysis of data from the pivotal clinical trials to measure the effect of the medication on the individual symptom of pain. Pain was among the symptoms measured as part of a composite primary endpoint; however, the studies did not pre-specify individual symptom scores as a secondary or tertiary endpoint. No published studies present contradictory evidence. To communicate the results of this post hoc analysis to prescribing physicians in a truthful and non-misleading manner, the company should disclose, among other things: (a) the omission of the effect of the drug on pain as a pre-specified primary, secondary or exploratory endpoint; (b) the post hoc nature of the analysis, and its consequent failure to meet FDA's standard for an adequate and well-controlled study; (c) the pre-specified primary endpoint(s) and the results; (d) the methodology for the post hoc analysis, including (i) whether the post hoc analysis was designed to test a pre-specified endpoint in accordance with a pre-specified analysis plan, and (ii) how the study controlled for confounding factors; (e) the results of the post hoc analysis, including the statistical significance and confidence intervals; (f) pertinent safety results shown in the post hoc analysis; (g) any other risks of bias not already specified with a retrospective data analysis; and (h) the post hoc analysis is not included in the product's labeling and FDA did not consider this analysis in approving the product. The company should summarize these disclosures in the oral or written communications, and can refer the health care professional to a website for more comprehensive information about the study. This scenario implicates Principle 4.

Scenario 5: A biopharmaceutical company conducts an open-label study in a population of 12 patients to evaluate the safety and efficacy of one of its oncology drugs for its approved indication. The study does not meet its primary safety end-point. Although the study meets one of several secondary efficacy endpoints, the result is not statistically significant. Because information about the one successful secondary endpoint is not based on scientifically- or statistically-sound methodologies, the company should not communicate this information outside of recognized contexts of scientific discourse and debate, which are outside of the scope of these Principles. This scenario implicates Principle 1.

Scenario 6: A biopharmaceutical company obtains FDA approval of a drug for treating lung cancer. The company conducts an adequate and well-controlled clinical trial for the product to determine whether it is a safe and effective treatment for pancreatic cancer. The clinical trial includes 100 patients. Of those 100 patients, half are tested with the company's product and the other half are tested with the standard of care product. In the standard of care arm, 50% of the patients achieve survival rates of more than one year, and the other 50% survive between six months and one year. In the testing arm of the study, 80% of patients achieve survival rates of more than one year and 20% of the patients survive for more than six months. Additionally, some patients in the testing arm develop liver and kidney failure, while none of the patients in the standard of care arm suffers those side effects. To communicate the results of this trial to a clinical practice guideline committee in a truthful and non-misleading manner, the company should disclose all of the above statistical information about safety and include appropriate descriptions and limitations of the study. This scenario implicates Principle 6.

Scenario 7: At a medical conference, a biopharmaceutical company hosts a product theater to describe new scientific research relating to one of the company's products. The new research includes information from post hoc analyses of sub-population data collected under the randomized, controlled clinical trials that formed the basis for the product's approval. This sub-population analysis was not a pre-specified endpoint of the trials. Neither the company nor any independent investigators have conducted randomized, controlled clinical studies evaluating the efficacy and safety of the drug on this sub-population. The FDA has not reviewed or expressed an opinion about the company's new research. To communicate this information at the product theater

in a truthful and non-misleading manner, the company should disclose, among other things: (a) the omission of the sub-population analysis as a pre-specified primary, secondary or exploratory end-point; (b) the post hoc nature of the analysis and its consequent failure to meet FDA's standard for adequate and well-controlled research; (c) the pre-specified endpoint(s) and the results of the study in the overall study population; (d) the methodology for the sub-population post hoc analysis (including how the study controls for confounding factors); (e) all the results of the post hoc analysis (including p values and confidence intervals); (f) any risk of various types of bias not already described; (g) pertinent safety results shown in the post hoc analysis; (h) any warnings and precautions in the product labeling that specifically apply to this sub-population; and (i) the absence of any FDA review of or opinion about this new research. The company should summarize these disclosures in the oral or written communications, and can refer the health care professional to a website for more comprehensive information about the study. This scenario implicates Principles 4 and 6.

Scenario 8: A biopharmaceutical company sponsored a phase 3 trial to expand the indication of one of its approved drugs to include rheumatoid arthritis (RA). Members of the company attend a physician medical association rheumatology conference. A principal investigator for the clinical trial sponsored by the company makes a podium presentation at the conference summarizing the results of the trial, and scientific staff of the company discuss the results with conference attendees. The scientific discourse described here is not subject to these Principles and should not be regulated by the FDA.

Scenario 9: In collaboration with a large health insurer, a biopharmaceutical company has evaluated the rate of hospitalizations for patients who use the company's cardiovascular drug for its indicated use, compared with the rate of hospitalizations for patients who use a competitor's drug, based on real-world evidence from the insurer's electronic medical records for over 200,000 adult patients nationwide. The data demonstrate that both the company's drug and the competitor's drug significantly reduced the rate of hospitalizations in patients ages 50-65. However, the competitor's drug demonstrated a higher rate of hospitalizations in this population. After communicating accurate and balanced information about use of the company's product in accordance with the approved labeling, to communicate this real-world data to additional payers in a truthful and non-misleading manner, the company should disclose, among other things: (a) the observational nature of this study, based on a review of the insurer's member data; (b) the study methodology and method(s) of statistical analysis; (c) any significant limitations of the data or the databases used; (d) the results of the study for both the manufacturer's drug and the competitor drug; (e) any pertinent safety results of this observational study; and (f) any risk of bias not otherwise described above. The company should summarize these disclosures in the oral or written communications, and can refer payers to a website for more comprehensive information about the observational study. This scenario implicates Principles 7 and 8.

Scenario 10: A biopharmaceutical company contacts a major health plan and requests an opportunity to present information regarding its oncology product pipeline. The company's slide presentation includes a timeline showing agents that are in Phase 3, Phase 2, and Phase 1 of development, with a one-page description of each study, including the study design and primary and secondary end points. The presentation is for the pharmacy and therapeutics committee of the health plan ("P&T Committee"), whose members include physicians and doctors of pharmacy. This is a highly sophisticated audience. The respective descriptions of the studies include results of primary and secondary endpoints and statistical significance but do not make statements that any of the drugs has been determined to be safe or effective. To communicate top-level pipeline information to the this audience in a truthful and non-misleading manner, the company should disclose, among other things: (a) the lack of FDA approval; (b) the possibility that FDA will not approve some agents in the pipeline; and (c) any material safety risks identified in the clinical studies conducted to date. This scenario implicates Principles 5 and 7.

Scenario 11: A biopharmaceutical company has submitted to FDA its NDA for an investigational oncology drug and expects approval within nine months. The company has scheduled meetings with the P&T committees of several pharmacy benefit managers and health plans to inform them that the product likely will be available within the year and to request that they consider placing it on their formularies promptly upon approval. To communicate information about the anticipated product indication, any limitations of

use, and the safety and efficacy data submitted to FDA as part of the application for approval in a truthful and non-misleading manner, the company should disclose, among other things: (a) the current status of the NDA; (b) the type of research that supports the safety and efficacy for the use of the product under consideration by FDA (with appropriate, context-specific disclosures regarding the specific research); (c) any FDA opinion on the sufficiency of the evidence; and (d) other relevant evidence that is necessary to an informed medical judgment, including any peer-reviewed contrary evidence. The company should make these disclosures as part of the oral or written communication. This scenario implicates Principle 7.

Scenario 12: A biopharmaceutical company contracts with a payer to acquire de-identified patient population data in exchange for a fair market value payment. The company then conducts a sub-group analysis on that data set. The company's analysis shows a correlation between the manufacturer's product and progression-free survival in African American patients. To communicate information about this sub-group analysis to the payer who provided the data, as well as to other payers, in a truthful and non-misleading manner, the company should disclose, among other things: (a) the study's reliance on a retrospective review of real-world evidence; (b) the observational nature of the study and the absence of a control group, resulting in the study's failure to meet FDA's standard for adequate and well-controlled research; (c) the absence of any FDA evaluation of the results; (d) the methodology for the sub-population post hoc analysis (including how the study controls for confounding factors); (e) any risk of various types of bias not already described; (f) pertinent safety results of this analysis; and (g) any warnings and precautions in the product labeling that specifically apply to this sub-population. The company should summarize these disclosures in the oral or written communications, and can refer the health care professional to a website for more comprehensive information about the study. This scenario implicates Principle 8

Scenario 13: Independent investigators have conducted a retrospective, meta-analysis regarding the safety and tolerability of a biopharmaceutical company's drug based on results from various randomized clinical trials conducted world-wide. The results of this meta-analysis are published in a peer-reviewed journal in accordance with all of the criteria set forth above. The company has reviewed the reprint and believes the analytical methodologies used by the investigators are scientifically sound. The company could distribute reprints of this journal article to health care professionals. In addition, to communicate information about the content of the reprint during sales representative calls to health care professionals in a truthful and non-misleading manner, the company should disclose, among other things: (a) accurate and balanced information about the approved product labeling (including the indication, limitations of use, efficacy and safety data described therein); (b) the type of research that is the subject of the reprint (including the study design, method of analysis, and appropriate, context-specific disclosures regarding the limitations with retrospective meta-analysis); (c) the results reported in the reprint, including the statistical significance and confidence intervals of each result; and (d) other relevant evidence that is necessary to an informed medical judgment, including peer-reviewed contrary evidence. The company should summarize these disclosures in the oral or written communications, and can refer the health care professional to a website for more comprehensive information about the study. This scenario implicates Principle 9.

Scenario 14: A biopharmaceutical company obtains FDA approval for a drug to treat cystic fibrosis. The Phase III pivotal study data are incorporated in the approved labeling and demonstrate statistically significant improvement in lung function. The data also show serious adverse events in 10% of the patients, including liver and kidney failure. The company can communicate the labeled data on improvement of lung function in discussions with health care professional, as well as in written materials, but also must include the information about safety risks in all such discussions and materials. All communications about the product should fairly balance the efficacy information with the risk information. This scenario implicates Principle 2.

Scenario 15: A large pharmacy benefit manager ("PBM") releases the results of comparative effectiveness research ("CER") that was based on a meta-analysis of various other studies that had previously been performed by payer-affiliated groups. The CER analysis supports using treatment options other than a biopharmaceutical company's product. The affected company has conducted its own health care economic analyses and outcomes research. The data from the company's research strongly refute the PBM's

CER. The company should be able to respond to the PBM's public statements about the company's drug with information from the company's research. To communicate such information in a truthful and non-misleading manner, the company should disclose, among other things: (a) the study methodology and method(s) of statistical analysis; (b) any significant limitations of the data or the databases used; (c) the results of the study for the manufacturer's drug and any competitor drugs (if applicable); (d) pertinent safety results of this analysis; and (e) any risk of bias not otherwise described above. The company should summarize these disclosures in the oral or written communications, and can refer health care professionals to a website for more comprehensive information about the company's research. This scenario implicates Principle 4.